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ON ADIPOSITY*

BY

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It is common knowledge that fat plays an integral part in the structure of most cells of the body, and in particular those in the central nervous system, but this lecture concerns itself solely with a group of cells which appear to have as their exclusive function the retaining and mobilizing of fat within the cell membrane. These cells produce the lard used in cooking, which the Greeks called aedeps—the parent word of adipose tissue. Adiposity thus implies an excess of fat in these cells. The more commonly used word "obesity," meaning excessive adiposity, is a nineteenth-century upstart. It was rarely used before this time, and even at the end of the eighteenth century, though the word was included in Johnson's Dictionary, no reference was given to its prior use. It means literally "to eat away," and Webster's Dictionary describes it as meaning lean that has eaten itself into fat. The increasing substitution of "obesity" for "adiposity" during the nineteenth century probably implies a renewal of a long-dead belief, among lay people at least, that adiposity was a disorder of metabolism and a state of ill-health.

In considering this subject, therefore, I have thought it wise to revert to the word adiposity, implying a consideration of those cells which are primarily concerned with fat metabolism.

The first question which arises is whether the cells have sufficient community of function to enable them to be treated as an organ. Without getting lost in the intricacies of semantic arguments, an organ can be defined as that part of the animal adapted by its structure for a particular function; the cells comprising it should be shown to be capable of reacting as a single unit, though admittedly parts of the organ may be isolated by disease and begin to act independently, as happens with adenomata and carcinomata.

It cannot be denied that the increase in adipose tissue seen at puberty, at the menopause, and as a result of excessive food intake, or that the decrease under conditions of starvation, affect the whole tissue so far as it can be examined. In certain lipodystrophies, however, in recurrent lipomata and Madelung's neck, restricted food intake depletes the unaffected part of the organ, while the diseased part retains its independence.

The idea that adipose tissue of the body behaved as an organ is by no means new, and was first advanced by Todt in 1870. Ever since this time anatomists, physiologists, and embryologists have returned to this concept. Wells (1940) pointed out that the cells from which adipose tissue is derived are developed from the main mesenchymal tissue and can be distinguished from other connective tissue cells. In their embryological state they have a gland-like structure and assume their adult signet-ring shape only when distended with fat. When emptied of fat they revert to the glandular structure, and indeed islets of glandular tissue found in sections of removed fat may give rise to diagnostic difficulties.

Wells (1940) has reviewed the whole subject, and it is difficult to escape his conclusion that this tissue embryologically, pathologically, and structurally behaves as an organ. It is proposed to treat the tissue as such, with the reservation that certain parts, such as the fat pads behind the eyes, the adrenal pad, and the sucking pad, may serve a different or additional function to that of being solely concerned with fat metabolism; to consider what is known about the structure and function of the adipose organ; and, finally, to pass from this to a consideration of those factors which affect its size.

Structure of the Adipose Organ

It has already been stated that the adipose organ is made up of cells capable of containing a large quantity of fat. The amount of fat in relation to water and protein varies greatly, from place to place in the body, and there are wide variations even when fat is taken from the same site. Fig. 1 shows the analysis of tissue taken from six lean subjects and seven obese subjects from approximately identical spots in the lower abdominal wall at operation. It can be seen that there is considerable variation in the constitution of the tissue from individual to individual. It will be noted that the amounts of water, fat, and protein are expressed as proportions of the weight of tissue removed. In order to imagine what happens when an individual passes from leanness to fatness, the organ must be considered as a whole. Increase in size of the organ—for example, to approximately double—would mean that there had been little increase in the total water content, an increase of almost 100% in the amount of fat, and, strangely enough, double the amount of protein. The latter point is of interest. Since it has been assumed that the cells in the organ do not increase in number in obesity, the protein increase probably represents

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additional protein available for metabolic exchanges taking place within the cells, though it is by no means certain that cells do not proliferate. These individual variations in fat, protein, and water content of adipose tissue, however, may be more apparent than real. If the organ were metabolically active, they might only reflect the previous food intake of the individual. It has been shown that the relationship between fat and nitrogen in adipose tissue taken from animals after a fast as compared with the tissue in the fully-fed state may vary greatly. In normal man the overall composition of the organ has been estimated by Keys and Brožek (1953) and others to be 62% fat, 14% water, and 24% cellular matter (Fig. 2).

The next question which arises is the size of the adipose organ in man. Many methods have been employed to estimate this. Whole-body dissections, and particularly the data from those carried out on reasonably normal subjects by Widdowson *et al.* (1951) and by Forbes *et al.* (quoted by Keys and Brožek, 1953), have formed the basic check for all other procedures, but such measurements are rare. Since fat has a quite different density from the remainder of the body (the lean-body mass), formulae derived from measurements of whole-body density have been used. Measurements of whole-body density can be made by contrasting the weight of the body in air and in water. The methods are complicated by the fact that they must include measurements of the volume of air in the lungs and an assessment of the volume of air in the gastro-intestinal tract.

Reynolds and Asakawa (1950) have employed an *x*-ray technique in adults for delineating and measuring subcutaneous fat, since most of the organ lies in the subcutaneous layers of the body (Wilmer, 1940). This technique had previously been used in children. A variation of this technique, using skin callipers to measure fat and skin thickness, has also been extensively employed.

Finally, as adipose tissue contains much less water than the rest of the tissues (the lean-body mass), formulae based upon the determination of the extracellular fluid and total body water in relation to body weight have been derived and used to measure the size of the organ. The whole subject has been admirably reviewed by Keys and Brožek (1953).

In summary, there is surprisingly good correlation between the data obtained by these different methods, and there can be little doubt that a reasonable estimate can be obtained of the size of the adipose organ in man.

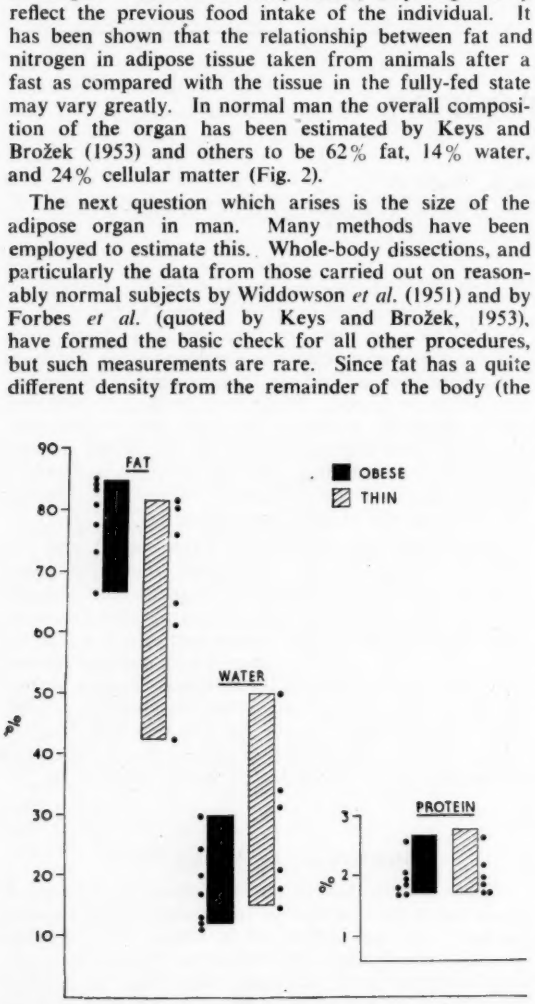

FIG. 1.—Analysis of biopsy material taken from lower right abdominal wall in six lean and seven obese subjects at operation.

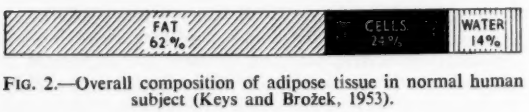

FIG. 2.—Overall composition of adipose tissue in normal human subject (Keys and Brožek, 1953).

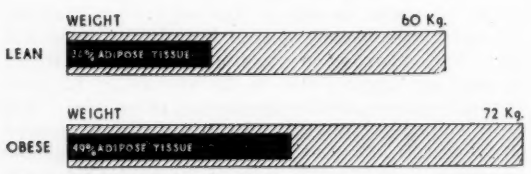

FIG. 3.—Comparison between adipose tissue in female subjects aged 40 with gain in weight of 20% due to adiposity.

TABLE I.—*Approximate Relationship Between Body Mass and Adipose Tissue in Man*

		Age 25	Age 40	Age 55
Males	Weight	70 kg.	70 kg.	70 kg.
	Adipose tissue	9·9 kg. (14%)	15·4 kg. (22%)	17·5 kg. (25%)
Females	Weight	60 kg.	60 kg.	60 kg.
	Adipose tissue	15·6 kg. (26%)	19·2 kg. (32%)	23 kg. (38%)

Table I has been compiled from the data obtained by these methods and represents the approximate size of the adipose organ in adults of the two sexes at different ages. For the sake of clarity no allowance has been made for the usual increase in weight occurring through the years. Males are regarded as having a weight of 70 kg. and females of 60 kg.

Table I shows that at all ages women have a larger adipose organ than men, and there can be little doubt that this is a true biological variant. The reasons for the increase in size with age are less certain. It may also be a biological variant, but, on the other hand, it has been contended by some that increase in weight with age, and therefore in the size of the organ, is neither biologically necessary nor desirable. At the moment there is insufficient evidence to decide this point, but the increase of size with age must be considered commonplace, at least in the Western world.

If any of these subjects were to become obese there would be no increase in the lean-body mass and no increase in the cell mass in adipose tissue. Thus, a total increase in weight would be represented by fat, except for 10–20% which might be represented by water. A woman of 40 weighing 60 kg. becoming 20% overweight would thus increase to 72 kg., of which the adipose organ would now represent 34 kg. Thus the proportion of body weight represented by fat would rise from 32% to 49% (Fig. 3).

The adipose organ, therefore, is very large indeed—representing about one-fifth to one-quarter of the total

body mass in normal subjects, and capable of increasing to over half the body mass.

Adipose tissue is usually thought to be poorly supplied with blood. This belief is probably based, firstly, on its pale colour as compared with muscle and, secondly, on the observation that it bleeds little at operation. Gersh and Still (1945), using a dye-injection technique and special staining methods, claim that in fact it has an extensive blood supply, which differs, however, in structure from that in other organs. It is composed of a loose network of very small vessels, and the authors have estimated that the capillary density in the adipose organ is at least equal to that of poorly supplied muscle. If, however, the capillary density be recalculated in terms of active metabolic tissue the blood supply is much richer than in most muscles.

Certain further details about the structure of the fat organ may be important. In the subcutaneous tissue the iodine number of the fatty acids decreases and the fat becomes more saturated as the sample taken gets further from the skin. This observation seems to imply that the organ is able to desaturate fatty acids (Henriques and Hansen, 1901 ; Wertheimer and Shapiro, 1948). Newborn infants have saturated fat at all levels, and this is thought to be concerned with the higher environmental temperature *in utero*. This change in saturation is also associated with a change in the physical properties of fat, and this in turn may be important in altering the rate of heat loss from the organism as a whole.

Functions of the Adipose Organ

There can be little doubt that the main function of the adipose organ is concerned with energy exchanges in the body. It shrinks when food supplies diminish and increases when there is excessive food intake. Furthermore, Newburgh (1942) pointed out that the diminution in size of the organ bore a relationship to the deficiency in calorie intake of the individual. Fig. 4 confirms the observation (Kekwick and Pawan, 1956).

Until recently the usual idea of the function of the adipose organ was that it was a static energy store, taking up surplus energy under conditions of excess eating, storing it in the form of fat, and giving it up when food intake was too little. Excessive size of the organ resulted from excessive calorie intake.

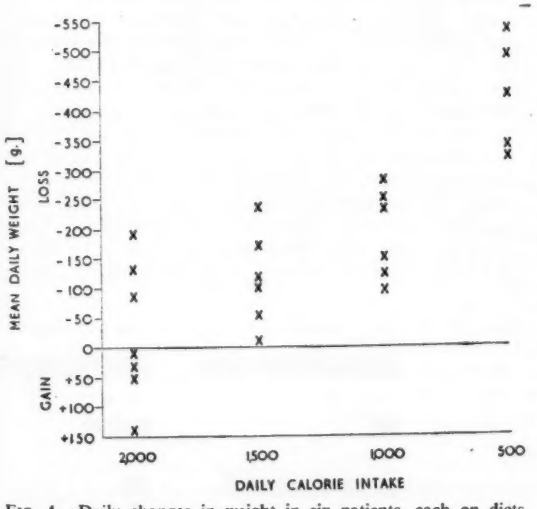

FIG. 4.—Daily changes in weight in six patients, each on diets of identical composition but different calorie value. (Mean figures of seven- to nine-day periods on each diet.)

The implication of this idea is that the fat depots take little part in the day-to-day and minute-to-minute metabolic changes going on in all tissues. If this were so, it is difficult to see why the adipose organ should have the large blood supply alluded to above, unless it be assumed that this was for use only in times of emergency.

Animal Studies

The classical concept of adipose tissue as an inert depot needs further examination to-day in the light of modern information obtained from *in vitro* studies of surviving strips of such tissue and recent extensive experimental work on animals. The *in vitro* studies of Shapiro and Wertheimer (1956) on surviving adipose tissue have shown that its oxygen uptake is high. It is also dependent on the previous nutritional state. Fatty tissue removed from a fasting animal has an oxygen uptake of 0.12 c.mm./hr./mg. After a period of fasting followed by a carbohydrate meal, the figure rises to 0.18 c.mm./hr./mg. (Mirski, 1942). That is to say that slices of adipose tissue have a metabolic activity about equal to that of kidney tissue and about half that of liver.

Extensive studies on intact animals, using deuterium or radioactive carbon as labels, indicate that half the adipose organ in normal rats and mice is metabolized and reconstituted in the incredibly short period of five to nine days (Bernhard and Schoenheimer, 1940 ; Stetten and Grail, 1943 ; Buchanan and Hastings, 1946). Certain hypothalamic lesions produce gross obesity to a point where the mice become about four times their normal weight (Mayer, 1957). The animals become voracious and even have to be prevented from choking themselves to death with food. The rate of turnover in the fat remains normal and the enlargement of the adipose organ depends on excessive deposition of fat. In certain congenitally obese animals, on the other hand, the same weight can be attained though the increase in appetite is less apparent. The obesity is produced in part by diminution in the rate of turnover, which slows down from a rate of five to nine days to a figure of about 90 days (Salcedo and Stetten, 1943). That alteration in the rate of turnover may affect the size of the organ is confirmed by the marked differences found in the amount of carcass fat as between the congenitally obese mice and the hypothalamic obese animals—when both are subjected to food deprivation sufficient to reduce them to the same weight (Hollifield and Parson, 1958) ; the carcass fat remaining much higher in the congenitally obese animals even though the total body weights are the same.

Such observations give a very different picture of the function of the adipose organ in animals. Far from being a comparatively static energy store for use in times of emergency, the organ appears to have a high metabolic activity, with a high oxygen uptake and a rapid rate of turnover. If these observations are accepted, the adipose organ must be taking part in the day-to-day energy exchanges of the organism as a whole.

Transposition of these figures direct to man give an astonishing picture. A normal woman of about 60 kg. weight at the age of 40, who had a fat-turnover of this

order, would be forming and destroying at least 1.5 kg. of fat every 24 hours. The intake of such a subject over the same period would probably comprise only some 60 g. of fat and about 400 g. of carbohydrate. If all the fat and half the carbohydrate in the diet were deposited as fat and exchanged in the adipose organ, this would account only for 150 g. a day—that is, 10% of the amount exchanged. The remaining 90% must presumably be synthesized from substrate brought to the organ by the blood-stream which is then being returned to the blood-stream in one form or another. This conclusion seems so unlikely that it must cast doubt on the techniques of estimating turnover rates. It has already been suggested by us that the most recently deposited fat may be most readily mobilized (Chalmers, Kekwick, Pawan, and Smith, 1958). If this were true a falsely high rate of turnover would be obtained from the interpretation of results using C14-labelled fatty acids recently administered.

It is fully realized that conclusions based on animal experiments do not always hold for man, and one must ask the question whether evidence exists to support the contention that such activity does indeed take place in man.

Studies in Man

No direct measurements of turnover using labelled fat have been made in the human subject, but there is abundant evidence in relation to the oxygen consumption of the adipose organ. It has already been pointed out that the obese only differ from the lean by the greater size of their adipose organ, and it is almost universally accepted that they have normal B.M.R.s. The B.M.R. is calculated from the oxygen uptake, an assumed figure for the respiratory quotient and expressed as a function of body weight and height (body surface). If fat were metabolically inactive the oxygen uptake of an obese subject should be comparable to that of a lean subject. If this were so, the B.M.R. in the obese therefore could be measured by taking the oxygen uptake, using the assumed respiratory quotient, and expressing this figure as a function of a lean subject of the same height but of normal weight. The carrying out of this procedure gives figures for B.M.R.s in the obese of the order of +20% to +50% (Strang, 1959). However, neither the cardiovascular, the respiratory, nor the central nervous system shows evidence of such unusual activity. The usual explanation, that the obese are under the strain of having to move their increased weight, does not hold under basal conditions. Indeed, under these conditions the obese are accepted as being less active, breathing more shallowly and less rapidly than normals, and having normal heart rates. The obvious explanation that the fat itself uses the extra oxygen appears to have been neglected.

If it is accepted that it does so, then adipose tissue in man has approximately the same oxygen uptake as the lean-body mass and its contained fluids—that is, about 0.2 c.mm./hr./mg., a figure comparable to the direct measurements of Shapiro and Wertheimer (1943) on isolated fat tissue of animals.

A further piece of indirect evidence also exists. The rate of turnover in the plasma of non-esterified fatty acids (free fatty acids) labelled with radioactive carbon has been measured in man. These substances, which probably represent the main form in which fat is conveyed from place to place in the body, are turned over in the blood-stream at an extremely rapid rate. Half the injected material is cleared from the blood-stream in one to three minutes, and one-quarter of the total plasma pool is therefore turned over every minute (Fredrickson and Gordon, 1958). This is many times faster than glucose; the comparable figures for the percentage turnover of the plasma pool a minute being approximately 0.7% for glucose and 28% for free fatty acids (Dole, 1960).

In summary, there appears to be direct evidence in animals and indirect evidence in man that the adipose organ is a highly active metabolic tissue with a turnover rate far more rapid than can be accounted for in terms of fat and carbohydrate intake.

Conflicting Hypotheses

It has been accepted that the main function of the adipose organ is almost certainly concerned with the energy needs of the body, since it shrinks under conditions of low energy intake and increases under conditions of high intake. It is from this point onwards that two conflicting points of view arise. The first is that the adipose organ is a relatively inactive calorie store, and the second is that the adipose organ is in a state of constant metabolic activity, taking part in the hour-to-hour and minute-to-minute metabolic changes of the body.

It is possible to examine indirectly which of these hypotheses is correct in two further ways. Firstly, where the total energy output of the body is known to be low, as in myxoedema, or after removal of the thyroid gland, the adipose organ should be normal in size under the first hypothesis if appetite is reduced commensurately with reduced energy output or greater than normal if appetite reduction has been insufficient. It would be unlikely to be less than normal. Under the second hypothesis, the adipose organ, however, might be expected to be reduced in size, as its function in relation to energy supply would be required to a less extent. Secondly, if exactly the same calorie intake in animals or man is maintained for a reasonable period of time, the resultant size of the adipose organ at the end should be identical in all under the first hypothesis but could only be different under the second.

Direct experimental evidence concerning the adipose organ after thyroidectomy was obtained by Mackay and Sherrill (1941). Three sets of adult rats were fed for 310 days on high-calorie and high-fat diets. The first acted as a control, the second were thyroidectomized, and the third were given thyroid extract. At the end of 310 days the weights of the control and thyroidectomized animals were the same, but carcass analyses showed that fat comprised 31.1% of the body weight in the controls and only 6.4% in the thyroidectomized animals. The results are illustrated in Fig. 5. (This may not hold when thyroidectomy is performed at a time when the animals are growing (Scow, 1951)—

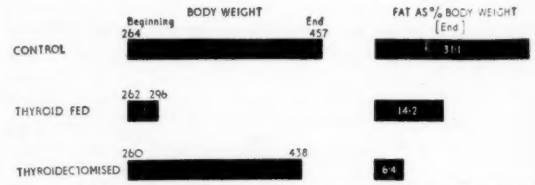

FIG. 5.—Body composition of three groups of rats after period of 310 days. Data of Mackay and Sherrill (1941).

an experimental result which accords with the observation that cretins tend to have an increase in body fat.)

There is also evidence in relation to this point in man. Plummer (1940) reviewed the nutritional state of 200 patients with primary myxoedema. He found that 38.5% of them were under standard weight for height and only 61.5% were either normal or above normal weight. It is recognized that some of the weight of these patients is represented by the deposition of myxoedematous tissue. As soon as these patients are given thyroid extract they go into negative nitrogen balance and rapidly shed the abnormal tissue. This rapid shedding of weight for the overweight group was measured. It represented an average of 5.9 kg. per person for the group as a whole, whereas the subjects on the average were only 4.6 kg. overweight. In short, Plummer concluded that hypothyroid patients were in fact grossly underweight when allowance is made for the myxoedematous tissue. It would appear, therefore, that, both in animals and in man, lowering of the metabolic activity of the organism as a whole is associated with a shrinking of the adipose organ. It is possible to argue that too much has been made of this shrinking in hypothyroid states, since the converse is manifestly untrue. None the less, the conclusion that the adipose organ decreases in states of low metabolic activity is probably important.

Evidence respecting alteration in size of the adipose organ when diets of equal calorie intake are given is

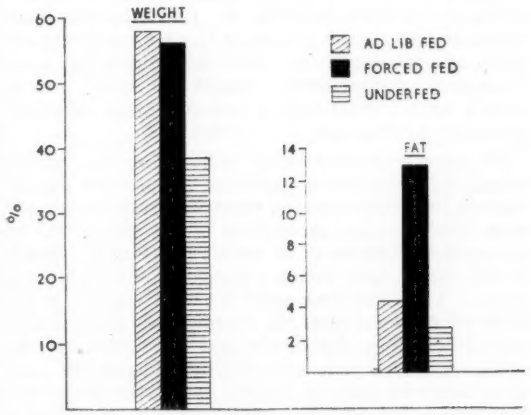

FIG. 6.—Changes in body composition of rats eating *ad lib.*, isocaloric force-fed rats, and underfed animals. Data of Cohn and Joseph (1959).

also available. The paired feeding experiments of Cohn and Joseph (1959) are impressive. One set of rats were allowed to eat *ad lib.* The amount was measured and a second set of animals were fed twice a day, by stomach tube, with exactly the same type and amount of food as the first. A third set were force-fed on 20% less food and acted as controls. At the end of the experiment the animals were sacrificed and analyses of the carcasses undertaken. The first and second sets of animals weighed the same at sacrifice, but the animals fed *ad lib.* had increased their body fat by 4.5%, though the force-fed animals having the same calorie intake had increased their body fat by 13.2%. The controls had less body fat and had gained less weight, as might have been anticipated. The results are illustrated in Fig. 6.

TABLE II.—*Comparison of the Effects of Repeated Injections of Saline, Non-fasting Urine Extracts (NF), and Fasting Urinary Extracts (F). Each Animal Was Given 0.5 ml. on Alternate Days for a 17-Day Period*

	No. of Animals	Mean Food Intake (% of Control)	Body Weight Change in g. Mouse Day	Carcass Analysis (% Body Weight)		
				Fat	Water	Protein
Saline ..	30	100	−0·109	13·5	64·3	11·9
NF ..	10	101	−0·118	13·4	63·7	11·8
F ..	20	98	−0·360	11·8	66·1	13·6

In reverse, Chalmers *et al.* (1958) have shown that after the injection of a urinary extract from fasting human subjects mice lose weight over a period of three weeks as compared with controls having either saline injections or urinary extracts from subjects who are feeding normally, even where the food intake of the

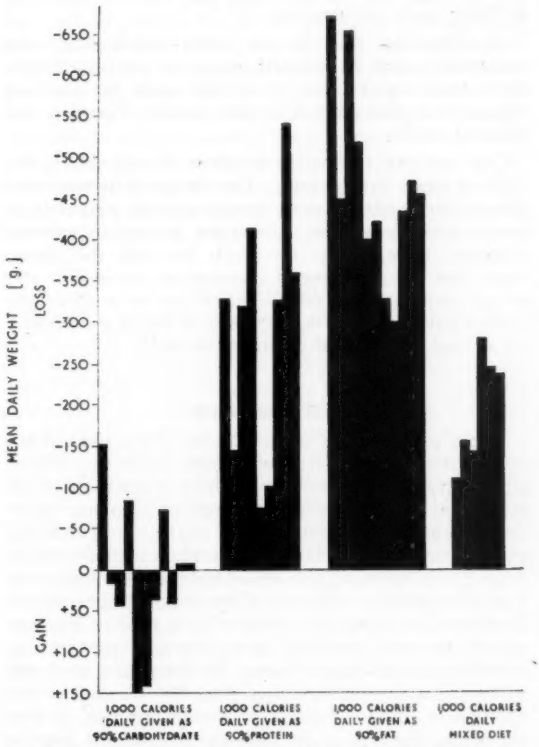

FIG. 7.—Daily loss of weight of patients on 1,000-calorie diets of different composition. (Mean figures of five- to nine-day periods on each diet.)

two sets is equal. Carcass analyses show this loss of weight to be about 70% fat and about 20–30% water (Table II).

In man, isocaloric diets fed to obese subjects in rotation produce different rates of weight loss over short periods (Fig. 7). Measurements were made of their food absorption, nitrogen balances, and total body water. It was concluded that some 70% of the weight lost in all groups is represented by loss of fat (Kekwick and Pawan, 1956, 1957). It would therefore appear as though the resultant size of the adipose organ in man may be changed after short periods on different diets of equal calorie value.

It was submitted theoretically that such findings could be made only if the adipose organ was in a constant state of activity, and it seems reasonable to conclude that this is indeed the case both in animals and in man.

If fat utilizes oxygen, then the organ almost certainly conforms to the present concepts of tissue behaviour (Brody, 1955)—namely, that oxygen is required for the synthesis of high-energy substances or bonds and that the breakdown of these with consequent energy release requires no oxygen. In most tissues some 70% of energy is released in the form of heat and the remaining 30% for the essential needs of the organ. It is now possible to speculate on what these special needs may be in the adipose organ. Energy would be required for synthesis of fatty acids—for releasing fatty acids for use by other organs (*Lancet*, 1959)—and possibly desaturating fatty acids within the adipose organ to maintain body temperature.

If substances exist in the organ which affect the percentage yield of essential energy as compared with heat energy, alterations in its size could be achieved without any alteration in oxygen uptake (Portman and Hegsted, 1957).

One can now review the problem of adiposity in the light of these conclusions. The simple statement that obesity arises when calorie intake exceeds output is of course unchallengeable. Under the present hypothesis, however, it represents the truth but not the whole truth, and the problems of increase or decrease in size of the adipose organ resolves itself into a study of the factors governing the laying down of fat in the adipose organ and the control of its mobilization.

Fat Deposition

Not a great deal is so far known about the control of fat deposition. There can be little doubt that almost all the fat taken into the body as food is deposited in the fat organ, even when administered in amounts below the calorie requirements of the organism (Rittenberg and Schoenheimer, 1935). In phloridzin-treated animals there is a sharp increase in blood lipid levels coincidental with a diminution of the size of the adipose organ, so that fat deposition does not appear to be a passive transference to the cells from the blood-stream. Furthermore, in isolated surviving fat tissue, fat deposition is shown to be halted by temperatures over 80° C. and by the addition of sodium fluoride or sodium cyanide, so that deposition appears to be an active metabolic process (Wertheimer and Shapiro, 1948).

There is little doubt, also, from *in vitro* studies of adipose tissue, that glycogen appears intracellularly in fat tissue if the animal has fasted for a period and then eaten carbohydrate. It precedes fat deposition and disappears coincidently with the cessation of fat formation (Tuerkischer and Wertheimer, 1942). These studies also show that the tissue has a respiratory quotient above 1, a finding that almost exclusively indicates the conversion of carbohydrate to fat. There seems little doubt, therefore, that carbohydrate can be, and probably is, a major precursor of fat. Single doses of insulin to animals fed normally leads to the appearance of glycogen in adipose tissue and the acceleration of fat deposition (Wertheimer, 1945).

In similar *in vitro* studies fasting has been shown to inhibit lipogenesis (Hausberger and Milstein, 1955). In view also of the work on obese patients already quoted (Kekwick and Pawan, 1956, 1957), it is interesting that Hausberger and Milstein found that the previous intake of a high-fat diet inhibited lipogenesis in isolated tissue removed from the animal.

In the intact animal there is ample evidence that a supply of food is necessary for fat deposition. It would appear that deposition largely ceases under conditions of starvation and increases where food intake is increased. This is not to say that appetite and satiety alone control fat deposition. The work of Cohn and Joseph (1959), already quoted, indicates that the manner in which the raw materials are supplied is certainly one other factor. Furthermore, studies on animals with hypothalamic lesions who get fat because of their voracious appetites show that the amount of fat laid down is much greater than that in control animals which have been force-fed the same amount of food (van Putten *et al.*, 1955). There must be many other factors related to fat deposition that are unknown, and it is clear that much more investigation will be needed before any coherent idea of this complicated process is achieved.

Fat Mobilization

Many gaps also exist in knowledge about the physiological control of fat mobilization. Studies with high-fat, high-protein, and high-carbohydrate diets suggest (Kekwick and Pawan, 1956, 1957) that the type of food influences the rate of fat mobilization, but the details of this are far from clear (Fig. 7). Hormones which are known to increase the amount of free fatty acid released from adipose tissue *in vitro* are adrenaline, noradrenaline, corticotrophin, growth hormone, and a urinary extract from fasting human subjects described previously by Chalmers *et al.* (1958).

We have been particularly interested in this urinary extract, partly because it appears to be important physiologically and partly because, by analogy with the way the body handles water, the control of the output side of the equation appears to be more important in relation to the total volume retained than control of the input factor. The conditions under which it appears in the urine are shown in Table III. Fasting, low-calorie intake, and carbohydrate deprivation give good yields of the substance. Two patients with diffuse lipoatrophy (one associated with diabetes mellitus and increased growth) have shown activity even when taking a normal diet. In six patients with deficient pituitary function, fasting has failed to give any yield at all, which would suggest that the pituitary plays an essential part in the chain of its production.

TABLE III.—*Conditions Which Govern Appearance of Fat-mobilizing Substance in Human Urine*

Present	Absent
Fasting	Normal diet
1,000 cal. (90% fat)	1,000 cal. (90% CHO)
2,000 ,, (80% ,,)	Hypopituitarism (fasting)
1,000 ,, (90% protein)	
Diffuse lipoatrophy (non-fasting)	
Diabetic ketosis*	
Carcinomatosis*	
Post-operative*	

* Were also on low-calorie and low-carbohydrate diets.

TABLE IV.—*Effects of Urinary F.M.S. in Mice*

Increases	Decreases
Liver fat	Body weight
Blood lipids	Carcass fat
,, ketones	Blood sugar
Fat utilization	

The biological properties of the substance are listed in Table IV. Injected into mice, it produces loss of weight, the loss being mainly in terms of the carcass fat and bearing some relation to the dose administered (Fig. 8). The food intake of the injected animals is the same as that for the controls injected with saline. It also produces rises in blood lipids, blood ketones, and liver fat within six hours of injection (Fig. 9), and is capable of liberating free fatty acids from an isolated fat pad (Chalmers *et al.*, 1960a). In structure it resembles, but is not identical with, corticotrophin (Chalmers *et al.*, 1960b), it is adsorbed on to oxycellulose, and has a weak melanophore-stimulating action. However, it is not identical with corticotrophin, since it exhibits none of the usual steroid-like effects in the intact animal, has only very low activity in releasing steroids from viable adrenal tissue, and after inactivation by hydrogen peroxide cannot be reactivated with cysteine. Nor does corticotrophin produce loss of fat in the intact animal.

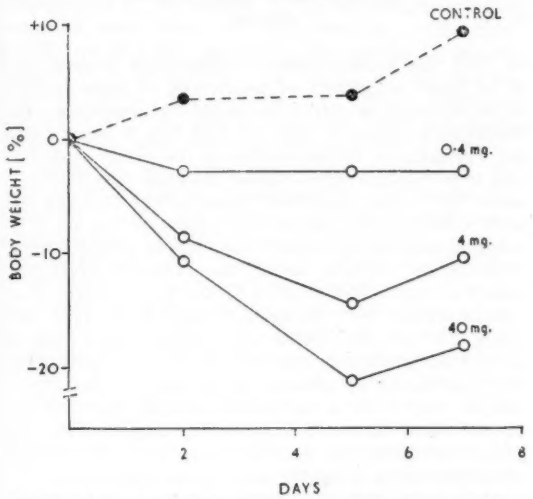

FIG. 8.—Loss of weight in mice after a single dose of F.M.S. in different doses. Food intake (g.): Control 7.0; 0.4 mg., 8.1; 4 mg., 7.9; 40 mg., 8.0.

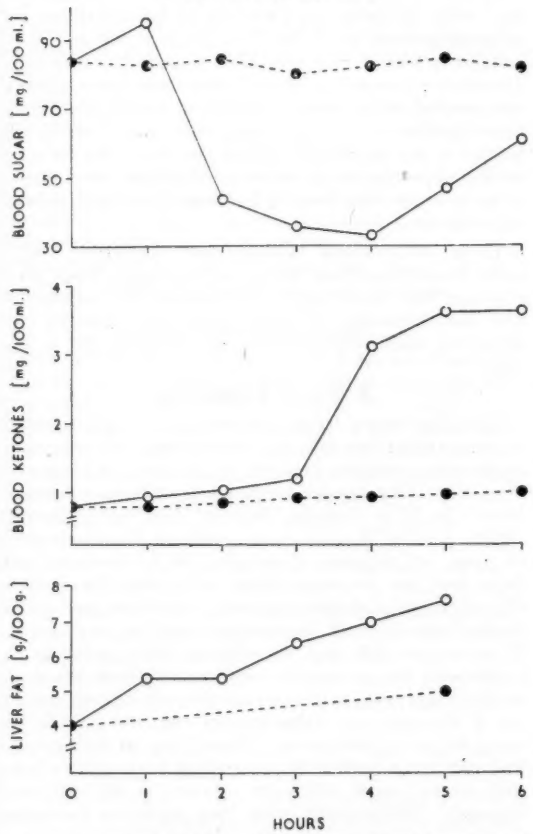

FIG. 9.—Effect of F.M.S. on blood sugar, blood ketones, and liver fat after injection into mice.

Fat mobilization itself probably mainly represents a release of free fatty acids from the adipose organ in view of the very rapid turnover of free fatty acid in the plasma pool (28% of the pool every minute), but these in turn can and do provide the major metabolic fuel for most tissues. Evidence has recently been put forward to suggest that fat may also be turned into carbohydrate, with a net gain of the latter substance (Kekwick *et al.*, 1959), and it is possible that part of the mobilization may take the form of converting fat into carbohydrate.

As with fat deposition, much more requires to be known of all these factors and the homoeostatic mechanisms which balance them before control can be exercised over the size of the adipose organ.

Conclusion

It cannot be pretended that these ideas of the structure and function of the adipose organ will stand the test of all further investigations and remain unchanged, since many of them are, of necessity, based upon imperfect evidence. It is only suggested that perhaps they are more nearly related to the true state of affairs than previously held views that fat exists as an inert calorie store. If so, the subject of adiposity becomes open to assault by different means than those previously employed.

The subject of adiposity is one of importance. It has been described as one of the major health hazards in modern life in the western world. Whether this be true or not, there is little doubt that people with enlarged adipose organs are unhealthy; that they die prematurely; that they are prone to diseases such as hypertension, diabetes, cholecystitis, and osteoarthritis; and that many of them are psychological cripples.

Public intolerance of this condition has never been so intense, as evidenced by the interest taken in the subject in almost every newspaper and magazine. This is in contrast to the somewhat resigned view taken by the medical profession of which Banting (1864) was complaining 100 years ago. Doctors too often tend to blame their long-term failure to relieve obesity on the gluttony of their patients. It is submitted that satisfaction with the too simple view that fat represents an inert calorie store has retarded and is retarding developments in this field.

It is difficult to express in full measure my gratitude to Dr. T. M. Chalmers and Mr. G. L. S. Pawan, who have worked so closely and happily with me on this problem, and whose work has stimulated many of the ideas incorporated in this article. I have also had help from many others, regrettably too numerous to mention individually, though I would like to single out Miss C. M. Evans, who has been responsible for much laborious secretarial assist-

ance. I thank the many patients who have been willing and ready to co-operate with us on every occasion on which they have been asked. I am also indebted to the President of the Royal College of Physicians of London for my election to the Bradshaw Lectureship.

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"There is prevalent amongst all Africans the injection craving." This perhaps originated from the fact that at the turn of the century there were outbreaks of diseases that could be cured or prevented by making scarification marks or by giving prophylaxis by injection and also curative measures by injections, e.g., yaws and N.A.B. or bismuth. This form of curative approach came near to the African's way of effecting cure for all sorts of diseases, which was by making scarification marks and breaking the surface of the skin and rubbing in medicine. The belief was that by so doing the medicine entered the blood and through this reached all the system. Thus an injection inserted into the buttock or into a vein carries a notion as near to the old belief as possible." (Dr. W. Ouko: 3rd Conference of East African Branch of the Society of Medical Officers of Health, *E. Afr. med. J.*, March, 1960.)

WHY THIOPENTONE INJECTED INTO AN ARTERY MAY CAUSE GANGRENE*

BY

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In 1948 the Swedish worker Schmiterlöw showed that if he made an extract of arteries or of veins from a horse or an ox the extract contained noradrenaline. His observations, however, did not lead him to suggest that the presence of noradrenaline in the artery wall had any importance, and no further attention was paid to it until 1957, when Burn and Rand showed that the day after rabbits were injected with reserpine the aorta no longer contained appreciable amounts of noradrenaline. Whereas the thoracic aorta from normal rabbits contained a mean quantity of 0.52 μg./g., the aorta from rabbits treated with reserpine contained less than 0.08 μg./g. It was also shown that while a spiral strip of aorta from a normal rabbit placed in an isolated organ bath contracted on addition of nicotine to the bath, a similar strip from a rabbit treated with reserpine did not contract. Burn and Rand (1958a) suggested that the constrictor action of nicotine was due to the release of noradrenaline from the store in the artery wall.

Another substance which was found to be inactive in the animal treated with reserpine was tyramine. Carlsson, Rosengren, Bertler, and Nilsson (1957) showed that while tyramine caused a rise of blood-pressure in an anaesthetized cat it failed to cause a rise of blood-pressure in a similar cat previously treated with reserpine. This observation was confirmed (Burn and Rand, 1958b), and several other amines related to tyramine, among them amphetamine and ephedrine, were shown to behave in the same way. While they were able to raise the blood-pressure in a normal animal, they were unable to do so in an animal which had been previously treated with reserpine.

These observations showed that substances which cause constriction may do so in two ways. They may constrict the blood-vessels themselves like adrenaline and noradrenaline, or they may act indirectly by liberating noradrenaline from the store in the artery wall.

Action of Thiopentone

There has been a series of recorded accidents in which an anaesthetist has injected thiopentone into an artery by mistake, probably because of the aberrant course of the artery. The incidence has been variously estimated from 1 in 8,000 (Lundy, 1942) to 1 in 55,000 (Cohen, 1948). Out of 24 cases, nine developed gangrene, and, of these, six required amputation of the forearm and three lost one or more digits. Professor Sir Robert Macintosh pointed these accidents out to me and asked whether the action of thiopentone could be investigated. It seemed possible that thiopentone might prove to be a substance which released noradrenaline from the store in the artery wall, and experiments were carried out to see if this was so. Observations were first made on spiral strips of rabbit aorta. When 2 mg. of thiopentone was added to a 5-ml. bath the strips of aorta contracted; they relaxed again when the solution in the bath was changed. Observations were then made by perfusing

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the isolated ear of the rabbit with a modified Ringer's solution. A cannula was tied in the central artery, and the solution entering the cannula then passed through the ear vessels and a record of the outflow was obtained. It was found that the injection of 25–50 μg. of thiopentone into the solution before it entered the artery caused a constriction of the vessels of the ear similar to that caused by small doses of noradrenaline. Our first thought was that the vasoconstriction might be due to the reaction of the solution; the solution of thiopentone which we injected had a *p*H of 8.65. When, however, we injected the same volume of Ringer–Locke's solution adjusted to the same *p*H there was no change in outflow.

In order to see if the vasoconstriction caused by thiopentone was due to the release of noradrenaline we applied three tests. The first was to repeat the injections of noradrenaline and of thiopentone after adding cocaine to the perfusion fluid. Cocaine is known to potentiate the vasoconstrictor action of noradrenaline. We found that cocaine also potentiated the effect of thiopentone and to the same extent. The second was to determine the effect of tolazoline (" priscol "). Tolazoline is known to abolish the constrictor action of noradrenaline, and we found that it abolished the constrictor action of thiopentone also.

Finally, we tested the action of thiopentone on the vessels of the ears of rabbits which had been treated with reserpine. The injection of reserpine removed the extractable noradrenaline from the ears, and we found that thiopentone had little or no constrictor action in them. All three tests gave results consistent with the idea that thiopentone caused constriction by releasing noradrenaline from the artery walls (Burn and Hobbs, 1959).

A substance with similar properties to thiopentone is hexobarbitone. There are, however, no records of gangrene after the injection of hexobarbitone into patients. We therefore tested its action on the vessels of the perfused rabbit ear. We found that it had almost no constrictor action—less than one-sixtieth of that of thiopentone. This finding supported the idea that the constrictor action in the rabbit ear was related to the production of vascular thrombosis and gangrene.

Effect of Sympathectomy

Some months later observations were described by Kinmonth and Shepherd (1959) in which they injected thiopentone into the central artery of the rabbit's ear while the animal was anaesthetized. They found that in the course of the next two weeks the terminal portion of the ear became gangrenous. They standardized their procedure, and, having injected a group of 20 rabbits, found that the mean area of gangrene produced was 14.5 sq.cm. Among other experiments, they removed the superior cervical ganglion and divided the great and posterior auricular nerves at the base of the ear. Having allowed time for the sympathetic fibres to degenerate, they injected thiopentone as before, and found that the area of gangrene produced was much less. The mean area in 20 rabbits was 8.8 sq. cm. Now when the sympathetic nerves to an organ have degenerated, Euler and Purkhold (1951) found that the noradrenaline which could be extracted from the organ was very greatly reduced. These results of Kinmonth and Shepherd's were therefore a further indication that the occurrence of gangrene was related to the presence of noradrenaline in the walls of the arteries, and was due to the release of this noradrenaline by the thiopentone.

Production of Gangrene in Tail of Mouse

The next step which was indicated was to study the occurrence of gangrene in animals treated with reserpine. I intended to do this in rabbits, but my colleague Dr. David McDougal suggested that we should try white mice. We found that if we injected a small volume, 0.04 ml. of a 10% solution of thiopentone under the skin of the tail, then signs of gangrene followed. We found it necessary to inject into the ventral surface of the tail, for injections on the lateral or dorsal aspects did not cause gangrene. It seemed likely that the injection had to be on the ventral side in order that the thiopentone should make contact with the artery.

Twenty-four hours after thiopentone injection into the tail of a mouse, examination of the tail showed necrosis at the site of injection, and the necrotic tissue often sloughed off, leaving an ulcer. Distal to the injection site a large part of the tail was cyanosed in almost all the mice. The region of cyanosis beyond the site of injection often made it difficult to distinguish the presence of a necrotic region. However, the ulcer following necrosis was easily seen and was recorded. At the end of 72 hours the cyanosed part of the tail showed signs of becoming stiff, while the ulcer remained as on the previous day. At the end of 96 hours the cyanosed part of the tail was gangrenous, being like a piece of wire.

Almost all control mice developed a gangrenous tail at the end of 96 hours. About 70% of the control mice developed an ulcer at the site of injection. In a small number of mice in which cyanosis was slight and in which there was no ulceration, the tail appeared almost normal at 96 hours.

Gangrene in Tail

The actual numbers and percentages of mice are recorded in Table I, in which the experiments have been divided into two groups according to whether reserpine was given once (24 hr.) or twice (24 and 6 hr.) before the injection of thiopentone. At 48 and 96 hours after thiopentone injection the differences between controls and reserpine-treated mice was significant (P less than 0.01) in both groups. Further, the difference between the percentage of gangrenous tails at 96 hours after one injection of reserpine and that after two injections of reserpine was also significant at the 1% level. The effect of reserpine was to delay the appearance of gangrene by about 24 hours in animals given two doses of reserpine, and by a somewhat shorter time in those given one dose. However, all tails that became cyanosed probably became gangrenous eventually, though we did not observe them after 96 hours. The number of mice without cyanosis was not different in the control and treated groups.

TABLE I.—*Proportion of Mice in Which Tails were Gangrenous 96 Hours After Injection of Thiopentone*

No. of Doses of Reserpine before Thiopentone. Each Dose = 10 μg.	Control Mice	Mice Treated with Reserpine Previously
1	55/61 = 90%	38/73 = 52%
2	56/68 = 85%	27/93 = 29%

Ulceration

The results for the occurrence of ulceration at the site of injection are given in Table II. The necrosis and ulceration were not so uniform in the control mice as

TABLE II.—*Proportion of Mice with Necrosis and Ulceration*

Time after Thiopentone	No. of Doses Reserpine	Control Mice	Mice Treated with Reserpine Previously
48 hours	1	24/42 = 57%	28/59 = 47%
72 ,,	1	32/60 = 53%	33/79 = 42%
96 ,,	1	30/61 = 49%	40/79 = 50%
48 ,,	2	49/85 = 58%	13/82 = 16%
72 ,,	2	57/85 = 67%	32/103 = 31%
96 ,,	2	54/72 = 75%	27/82 = 33%

was the occurrence of gangrene. Thus ulceration was recorded in 50–60% of the first group, whereas in the second group ulceration was recorded in 75%. One injection of reserpine before thiopentone gave no protection against ulceration, as Table II shows, but two injections gave protection, the difference between treated and control mice being significant (P less than 0.01) at 48 hours, 72 hours, and 96 hours. There was no significant difference in the incidence of necrosis or gangrene between the mice which were given no reserpine after thiopentone injection and those which were given three injections of reserpine *after* thiopentone injection.

These results show that the changes produced by thiopentone at the end of 96 hours affected a much smaller percentage of mice which received beforehand two injections of reserpine. So far as gangrene was concerned it seemed likely that the development was only delayed, and that it would have appeared in a higher percentage of mice at the end of 120 hours. But there was no similar progressive development of necrosis and ulceration, for the number of mice affected did not significantly increase after 72 hours. Thus two injections of reserpine had a protective action (Burn and McDougal, 1960).

Discussion

There are now three pieces of evidence concerning the production of gangrene by thiopentone. First, thiopentone has a vasoconstrictor action, which is due to the release of noradrenaline from artery walls (Burn and Hobbs, 1959). Second, partial protection against gangrene is obtained after degeneration of the sympathetic fibres (Kinmonth and Shepherd, 1959). Protection obtained in this way may be due to the disappearance of noradrenaline from the vessels when the sympathetic fibres degenerate. Third, considerable protection against gangrene is obtained by treating the animal with reserpine beforehand. This protection may also be due to the disappearance of noradrenaline from the vessels (Burn and Rand, 1957, 1958a).

That noradrenaline when liberated by thiopentone can produce gangrene is made likely by the evidence that noradrenaline infusions have led to necrosis of the skin. Kepes, Haimovici, and Simon (1954) and Shapiro and Perlow (1956) have described skin necrosis and ulceration in patients after intravenous infusion of noradrenaline (4 μg./ml.) for periods of 48 hours. The necrosis was not around the site where the needle was introduced, but at some distance from it. Skin necrosis has also been produced in dogs and rabbits. Finally, it may be said that the liberation of noradrenaline by thiopentone is probably a local release in the vessel-wall rather than a release into the blood-stream.

Summary

If thiopentone is by accident injected into an artery, gangrene may occur in the part supplied by the artery.

Thiopentone has been shown to cause vasoconstriction in the perfused rabbit ear, and this appears to be due to the release of noradrenaline from the artery walls. The constriction is increased by cocaine, abolished by tolazoline, and is very small or absent in preparations from reserpine-treated animals.

Gangrene has been produced in the tail of the mouse by injecting thiopentone. It was accompanied by necrosis and ulceration at the site of injection. These changes were much less frequent in mice pretreated with reserpine. The administration of reserpine causes the disappearance of noradrenaline from the artery walls. Hence thiopentone appears to cause gangrene because of the local release of noradrenaline.

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A SURVEY OF THE EPILEPSIES IN GENERAL PRACTICE

A REPORT BY THE RESEARCH COMMITTEE OF THE COLLEGE OF GENERAL PRACTITIONERS*

Epilepsy has been recognized as a disease from the dawn of history. It is a common and often a dramatic malady, and yet accurate figures of its incidence are difficult to collect. Parents and relatives are only too willing to forget such happenings in their children. The admission of "blackouts" debars one from a driving licence, and may even prevent emigration. Insurance policies may be loaded, and the history of fits may make employment difficult to find. Personal factors such as these tend to make people deceptive about the illness, both in themselves and in their kinsfolk. Lord Cohen (1958) suggested that there were between 2 and 4 epileptics per 1,000 of the population; a figure borne out by Logan and Cushion (1958), who estimated the figure at 3.3 persons per 1,000. Lesser and Hunt (1954) suggest that the figure in the U.S.A. lies between 4 and 5, but there is a dearth of accurate figures; indeed, Brain (1951) quoted the findings of Gowers published some 50 years before. Tizard (1955) in a chapter on the subject gives no figures of incidence.

Another difficulty in the assessment of epilepsy is that patients in the various age-groups are usually referred to different consultants. Children are sent to the paediatrician, the aged to the geriatric specialist, and

*Members of Working Party: Dr. D. L. Crombie, Dr. K. W. Cross, Dr. J. Fry, Dr. R. J. F. H. Pinsent, Dr. C. A. H. Watts (recorder).

adults to the general physician, the neurologist, or the psychiatrist. Some never reach a specialist at all. The majority of epileptics in the community are likely to be seen only by the family doctor. Because of the unique position of the general practitioner, it was decided to attempt to collect figures at general-practice level.

In the planning of the survey, difficulties were encountered in defining epilepsy. It was decided that the subject should be covered as widely as possible. The following definition suggested by Dr. Denis Williams was used by us. "Epilepsy for our purpose will include all attacks primarily cerebral in origin in which there is a disturbance of movement, feeling, behaviour, or consciousness. It will therefore obviously not include fainting, aural vertigo, or psychologically determined attacks."

It was decided to write two papers on the findings of the survey—namely, a statistical analysis and a clinical appraisal. This present paper confines itself to the statistical aspect of the study, and it attempts to answer the following questions.

1. What is the incidence of epilepsy in the community? How is it distributed by age and sex?

2. What is the employability of epileptics, and what proportion of them have their fits adequately controlled? How many need to be cared for in an institution?

3. What is the pattern of treatment prevalent in general practice?

4. What proportion of cases are referred by the general practitioners to the consultants?

Method

The survey began on October 1, 1957, and ended on September 30, 1958. During this period 134 general practitioners from 67 practices in England and Wales collected details on specially designed record cards of all persons who had had a fit or a convulsion of any kind. Sample surveys in Scotland and South Australia took place at the same time. Two main groups of cases were recognized.

1. *First Fits.*—All patients having the first fit of their life during the survey year were collected into this section.

2. *Chronic Epilepsies.*—This larger group consisted of all patients who had had repeated fits, or who had been under continuous treatment for fits within two years of the start of the survey. This section was further subdivided into those who had had a major attack which is an easily recognizable event, and those who had other forms of epilepsy such as petit mal, temporal-lobe attacks, or feelings of unreality, and so on. These other attacks are often much more difficult to recognize and to define. Observers were asked to describe the attacks in full rather than to label them. Patients who had had both kinds of seizure were included in the major epilepsy group.

When the record cards were scrutinized one or two cases of sleep paralysis and breath-holding attacks were accurately described and classified as "other attacks," but these were not included in the series. A few other cases were rejected. For instance, there were some patients who in the past had on the evidence of a single fit been labelled as cases of chronic epilepsy. In the absence of E.E.G. evidence of epilepsy, such cases were not included. Furthermore, 79 cards had been completed for patients who were known to have had a series of fits in the past, but at the time of the survey were no longer having attacks, nor any treatment to prevent fits. These cases, too, were excluded from the survey.

The distribution of the practices in England and Wales is shown in Fig. 1. It shows that cases were collected from most parts of the country, but the density of the collecting practices does not coincide with the population distribution of the country as a whole.

FIG. 1.—Map showing the distribution of the 67 practices of the survey in England and Wales.

Incidence of Epilepsy

The findings of groups of general practitioners in both Scotland and South Australia are of interest, but the samples are too small to be really representative of those countries. The prevalence rates are shown in Table I. It should be noted that in the subsequent discussion only the figures for England and Wales are used. In this main survey a total of 1,391 persons had fits of some sort or were treated for the same during the survey year. Chronic epilepsy accounted for 1,209, and 182 had their first fit during that period. The prevalence of epilepsy in England and Wales was therefore 4.19 persons per 1,000, with a slight predominance among males. First fits occurred in 0.63 per 1,000 of the population. Details of these figures are given below.

TABLE I.—*Distribution of the Samples by Sex and Type of Fit, Related to the Populations at Risk*

Population at Risk	Sex	First Fits			Chronic Epileptics			Grand Total
		Major	Other	Total	Major	Other	Total	
England and Wales								
288,830	M	75	19	94	509	110	619	713
	F	67	21	88	450	140	590	678
	P.	142	40	182	959	250	1,209	1,391
No. per 1,000	P.	0·49	0·14	0·63	3·32	0·87	4·19	4·82
Scotland								
18,116	M	4	1	5	30	7	37	42
	F	1	0	1	30	6	36	37
	P.	5	1	6	60	13	73	79
No. per 1,000	P.	0·28	0·06	0·34	3·32	0·72	4·03	4·36
South Australia								
13,000 approx.	M	5	0	5	9	0	9	14
	F	8	0	8	9	5	14	22
	P.	13	0	13	18	5	23	36
No. per 1,000	P.	1,00	0·00	1·00	1·38	0·38	1·77	2·77

It was evident that major epilepsy was much more common or at least more frequently recognized than the other forms of the disease, accounting for some four-fifths of all the cases. There was a predominance of males in the major group, but more females had other types of epilepsy, so that the total for the chronic cases was very similar in both cases. These figures are shown in Table II.

TABLE II.—*Incidence of Fits by Type and Sex (England and Wales)*

	Males	Females	Total
Grand mal ..	509 (42%)	450 (37%)	959 (79%)
Other types ..	110 (9%)	140 (12%)	250 (21%)
Total	619 (51%)	590 (49%)	1,209 (100%)

TABLE III.—*Comparison of 1957 Population of England and Wales with Practices of Known Age-structure*

Age-group	Males		Females	
	Pop. of E. and W. (%)	Pop. of Sample (%)	Pop. of E. and W. (%)	Pop. of Sample (%)
0–4 ..	7·89	8·26	6·97	6·90
5–9 ..	8·17	8·68	7·27	7·54
10–14 ..	8·21	8·41	7·29	7·24
15–24 ..	12·74	12·13	11·93	13·07
25–34 ..	14·02	14·86	13·06	14·68
35–44 ..	14·43	15·61	13·88	13·92
45–64 ..	24·98	23·01	25·86	23·67
65+ ..	9·56	9·04	13·74	12·98
Totals ..	100·0 (21,648,000)	100·0 (26,815)	100·0 (23,259,000)	100·0 (28,605)

A complete age and sex distribution was available for 20 practices, and Table III shows the age and sex breakdown of these practices as compared with figures for the country as a whole. As these distributions are very similar, it was thought justifiable to work out prevalence rates in our series, using the distribution of population in England and Wales for 1957. The numbers of chronic epileptics per 1,000 related population by age and sex are given in Table IV and illustrated in Fig. 2.

Fig. 2 shows a maximum incidence of chronic epilepsy in the decade of 15–24 years. The sex incidence was almost equal except for a predominance of males in the 10–14 age-group and again in old age. The male excess in the senile group and the trend of the histogram is confirmed by the figures of Logan and Cushion (1958). It should be noted that among schoolchildren the epilepsy rate was about 4 per 1,000; a very much higher figure than that of 0.62 given by Pirrie (1952) for London schoolchildren. The pattern for epileptics with "other types" of fit was based on rather small figures for individual age-groups.

TABLE IV.—*Distribution of Chronic Epileptics per 1,000 by Age and Sex*

Age-group	Estimated Distribution of Survey Population	Major		Other		All Chronic	
		No.	Rates/1,000 Population	No.	Rates/1,000 Population	No.	Rates/1,000 Population
Males							
0–4 ..	10,986	29	2·64	4	0·36	33	3·00
5–9 ..	11,375	42	3·69	8	0·70	50	4·39
10–14 ..	11,431	42	3·67	16	1·40	58	5·07
15–24 ..	17,738	78	4·40	26	1·46	104	5·86
25–34 ..	19,521	97	4·97	10	0·51	107	5·48
35–44 ..	20,091	81	4·03	13	0·65	94	4·68
45–64 ..	34,781	95	2·73	24	0·69	119	3·42
65+ ..	13,311	45	3·38	9	0·68	54	4·06
All ages ..	139,234	509	3·66	110	0·79	619	4.45
Females							
0–4 ..	10,427	24	2·30	8	0·77	32	3·07
5–9 ..	10,876	30	2·76	12	1·10	42	3·86
10–14 ..	10,905	20	1·83	10	0·92	30	2·75
15–24 ..	17,847	83	4·65	28	1·57	111	6·22
25–34 ..	19,537	85	4·35	17	0·87	102	5·22
35–44 ..	20,764	63	3·03	19	0·92	82	3·95
45–64 ..	38,686	102	2·64	30	0·77	132	3·41
65+ ..	20,554	42	2·04	16	0·78	58	2·82
N.K. ..		1				1	
All ages ..	149,596	450	3·01	140	0·93	590	3·94

First fits occurred mainly in the youngest age-group. The sex incidence was almost equal except in old age, where again there was an excess among males. The figures are shown in detail in Table V and Fig. 3.

Miller *et al.* (1960) showed that in the Newcastle upon Tyne 1,000 Family Survey the onset of convulsions was most common in the first two years of life. Table VI

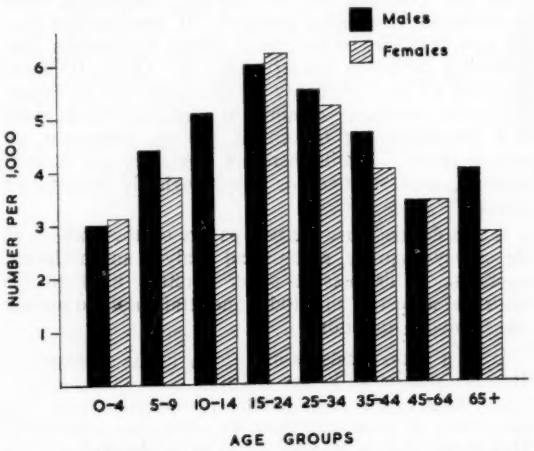

FIG. 2.—Numbers of chronic epileptics per 1,000 by age and sex.

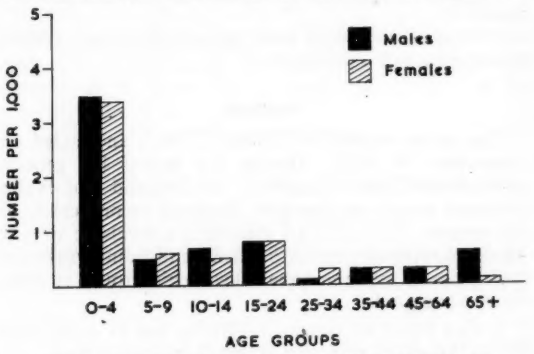

FIG. 3.—Numbers of first fits per 1,000 by age and sex.

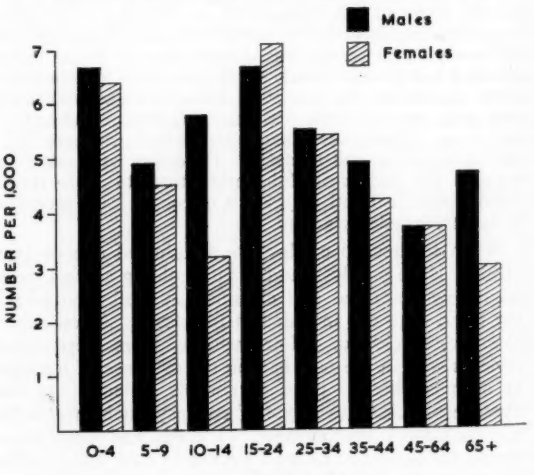

FIG. 4.—Total number of persons having fits per 1,000 by age and sex.

TABLE V.—*Distribution of First Fits per 1,000 by Age and Sex*

Age-group	First Fits: Major No.	Major Rates/1,000 Population	Other No.	Other Rates/1,000 Population	All First No.	All First Rates/1,000 Population
Males						
0–4 ..	33	3·00	6	0·55	39	3·55
5–9 ..	4	0·35	2	0·18	6	0·53
10–14 ..	6	0·53	2	0·17	8	0·70
15–24 ..	12	0·68	3	0·17	15	0·85
25–34 ..	3	0·15	0	0·00	3	0·15
35–44 ..	4	0·20	2	0·10	6	0·30
45–64 ..	7	0·20	2	0·06	9	0·26
65+ ..	6	0·45	2	0·15	8	0·60
All ages ..	75	0·54	19	0·14	94	0·68
Females						
0–4 ..	28	2·69	7	0·67	35	3·36
5–9 ..	6	0·55	1	0·09	7	0·64
10–14 ..	2	0·18	3	0·28	5	0·46
15–24 ..	12	0·67	3	0·17	15	0·84
25–34 ..	4	0·20	2	0·10	6	0·30
35–44 ..	3	0·14	3	0·14	6	0·28
45–64 ..	9	0·23	2	0·05	11	0·28
65+ ..	3	0·15	0	0·00	3	0·15
All ages ..	67	0·45	21	0·14	88	0·59

TABLE VI.—*Distribution of First Fits in the First Five Years of Life Compared with the Newcastle upon Tyne Survey*

Year of Life:	1	2	3	4	5	Total
Newcastle survey	20	16	12	9	4	61
C.G.P. ,, ...	23	23	18	6	4	74

compares the figures for the two surveys, and shows a clear similarity. In our series there was a slight predominance of males over females.

Fig. 4 shows the total incidence of first fits and chronic epileptics in the various age-groups. This showed that fits of all kinds were most likely to occur during the pre-school years, and between 15 and 24 years. There was a slight tendency for fits to increase in incidence in old age among males.

Employability of Chronic Epileptics

Excluding children under 15 and retired persons, cases were classified into four categories including a small group who were unemployed for reasons other than epilepsy.

Fully Employed.—These were men and women who did normal work, and to whom epilepsy was no handicap so far as employability was concerned. It also included the housewife who did her full housework unassisted.

Partially Employed.—These were patients whose work had to be modified considerably because of their fits. At home the housewife could only do restricted work; and, outside, sheltered employment was necessary.

Unemployed.—These unfortunate people were unemployable because of the severity and frequency of their fits, through mental deterioration, or for social reasons.

Table VII shows that about three-quarters of chronic epileptics of employable age were fully at work and unembarrassed by their condition. Some 8% were unemployed or unemployable because of epilepsy, and a further 12% were only capable of restricted work. In other words, in England and Wales there must be about 11,500 persons unemployed because of epilepsy.

TABLE VII.—*Employability of Chronic Epileptics*

Employability	Number	Percentage
Fully employed	699	74·4
Partially	110	11·7
Unemployed because of epilepsy or related social reasons	74	7·9
Unemployed for other reasons	57	6·0
All epileptics of employable age ..	940	100·0

Admission to Hospital

Table VIII shows the place of care for patients in the whole series. Those who were in hospital were not necessarily long-stay patients, some having been admitted for investigations and so on.

Only 3.6% (43 patients) suffering from epilepsy required to be treated in hospital during the survey year, but there must also have been some patients in institutions who had been there for many years, and so were no longer in the practices under study. It must also be realized that some of the 43 cases may only have been admitted for a period, to adjust drug therapy, to complete some investigations, or to give the relatives a break from a difficult invalid. Only a small proportion of epileptics seemed to need institutional care. D. A. Pond (to be published) suggests that probably 10% of cases will need hospital care at some period of their lives.

TABLE VIII.—*Place of Care by Sex for Patients with First Fits and Chronic Epilepsy*

Place of Care	Sex	First Fits: Major	First Fits: Other	Chronic Epilepsy: Major*	Chronic Epilepsy: Other
Institution	Males ..	0	0	21	2
	Females ..	4	0	13	7
	Total	4	0	34	9
At home	Males ..	75	19	488	108
	Females	63	21	436	133
	Total	138	40	924	241

* Excluding one female with unknown place of care.

TABLE IX.—*Incidence of Social Problems by Sex*

	Males	Females	Total
No social problem	496 (80·1%)	487 (82·5%)	983 (81·3%)
A ,, ,, ..	115 (18·6%)	86 (14·6%)	201 (16·6%)
Not known ..	8 (1·3%)	17 (2·9%)	25 (2·1%)
Total ..	619 (100%)	590 (100%)	1,209 (100%)

Incidence of Social Problems

Pond investigated a sample of the practices in this survey to assess the incidence of social problems among epileptics. A full account of this work is to be published elsewhere. On the form for our survey the question was asked, "Is there a social problem?" The figures resulting from this question are given in Table IX.

Social problems were shown to occur on average in some 17% of the cases. They were slightly more frequent among males than among females. Pond gives the figure at 29%, which he suggests is on the low side. Some difference in the two assessments was to be expected as the object of the Pond survey was to estimate the incidence of social problems both apparent and hidden, and his psychiatric social worker spent a great deal of time with each case. This sort of investigation would be bound to uncover problems which would not be obvious to the family doctor who was not particularly looking for them.

Control of Fits

The general practitioners in the survey were asked to determine at the end of the survey year if the fits in

chronic epilepsy had been completely controlled; if not, to record whether the patient had had one or more than one fit during the year. This information gave a crude figure showing the degree of control. Table X shows the assessments.

These figures show that 44% of grand mal epileptics had their fits completely controlled during the survey year, but only 32% of other types were treated with such success. Some 40% of all epileptics had more than one fit during the year. Table XI shows the number of fully employed persons in relation to the number of their fits. It can be seen that a total of 329

TABLE X.—*Control of Fits by Type of Fit in Chronic Epileptics*

	Major Epileptics		Other		Total	
	No.	%	No.	%	No.	%
Completely controlled ..	424	44·2	81	32·4	505	41·7
One fit only in the year ..	123	12·8	23	9·2	146	12·1
More than one fit	353	36·8	134	53·6	487	40·3
Not known ..	59	6·2	12	4·8	71	5·9
Total ..	959	100·0	250	100·0	1,209	100·0

TABLE XI.—*Control of Fits in Fully Employed Persons by Type of Fit and Sex*

	Males		Females		Total	
	Major	Other	Major	Other	Major	Other
No fits	149	21	141	28	290	49
One fit during survey year ..	38	5	36	11	74	16
More than one ..	69	35	90	44	159	80
Not known ..	14	3	10	4	24	7
Total fully employed ..	270	64	122	41	547	152
Total full housework ..	—	—	155	47		

(47%) fully employed persons had one or more fits during the survey year, but this did not prevent their being fully and usefully employed, probably without any stigma of epilepsy attached to them.

Pattern of Treatment

In this survey no attempt was made to assess the therapeutic efficacy of the various drugs used. The question for which an answer was sought was simply this, "What kind of drugs were used by family doctors in the treatment of epilepsy during the year 1957–8?" A statistical evaluation of therapies was not practicable, because there were so many possibilities of combinations and changes during the survey year. Phenobarbitone, either alone or in combination, was clearly the favourite anticonvulsant. It was about two and a quarter times as popular as phenytoin sodium. Next in popularity was primidone, and a long way behind troxidone, methoin, acetazolamide, amphetamine, and bromide in that order. The last was used in only 15 cases as compared with 1,000 receiving phenobarbitone. Troxidone was the only drug to be used more often with other types of epilepsy than with grand mal.

Proportion of Patients Seen by a Consultant

As has been stated, there is at present no single channel for epileptics seeking specialist advice. A variety of consultants are concerned, but general practitioners have the greatest opportunity of seeing cases in the community. Even they will not identify every case, as unusual types are often difficult to diagnose correctly,

TABLE XII.—*Proportion of Cases Referred to Consultant by Type of Fit*

Referred	First Fits				Chronic				Total	
	Major		Other		Major		Other			
	No.	%	No.	%	No.	%	No.	%	No.	%
During survey	65	45·8	23	57·5	57	5·9	25	10	170	12·2
Before ,,	—	—	—	—	604	63	161	64·4	765	55
Not referred or not known	77	54·2	17	42·5	298	31·1	64	25·6	456	32·8
Total ..	142	100	40	100	959	100	250	100	1,391	100

and many patients who have minor attacks never report their problems to a doctor at all.

In this survey the family doctors were asked if cases under their care had been referred to a hospital or a consultant at any time, either before or during the survey. The answers to this question are shown in Table XII. It can be seen that about one-half of the first fits which are major attacks are not referred to a specialist. Most of these are probably febrile convulsions in children, and, unless repeated, the average family doctor feels any benefit of complete investigation will be offset by an increase in parental anxiety. Other types of fits, including petit mal, are likely to be repeated and thus demand fuller investigations, and the survey shows that almost 60% of such cases were in fact referred to a consultant. Chronic epilepsy is a long-standing disease, and many of the patients may have been referred to a specialist before the survey, unknown to their present G.P. Thus the estimate that between a quarter and a third of chronic cases have never seen a consultant may be rather high, but it is likely that not more than three-quarters of all patients suffering from epilepsy are passed on to the specialist. This underlines the importance of studying the subject at G.P. level, where the majority of cases are seen.

Discussion

This survey shows that in England and Wales the average number of first fits over the survey year was 0.63 per 1,000. Chronic epilepsy amounted to 4.19 per 1,000. A slightly lower incidence was obtained from the practice in Scotland (4.03 per 1,000), and a much lower incidence from the South Australian practices (1.77 per 1,000).

How accurate and representative are these figures? There is a marked difference in the number of epileptics per thousand in the different practices, varying between the extremes of 1 and 12 (Fig. 5). Doctors at the extremes were questioned, and it seems that there was

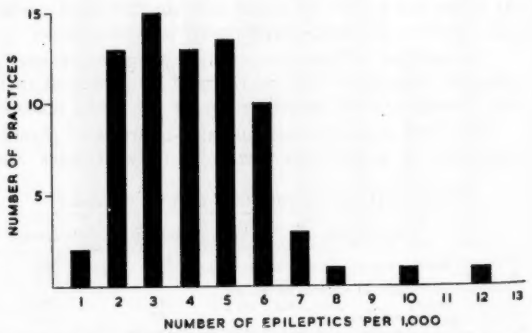

FIG. 5.—Proportion of chronic epileptics per 1,000 as shown in the different practices.

a real difference in the prevalence of the epileptics from practice to practice. Logan and Cushion's (1958) figures reveal that there is a tendency for the disease to be more prevalent in the lowest social grades. No attempt was made to effect social grading in this survey, but the practices with the high figures tended to come from lower-working-class practices, and, conversely, the lowest figures occurred in residential types of practice. The highest incidence of all was found in a practice with a large annual turnover, where the doctor had a special interest in epilepsy. The circumstances of this practice tended to filter off epileptics on to his list, giving an abnormally high figure.

Many patients who have major attacks also suffer from other forms of the disease. They have intense feelings of unreality, panic attacks due to ictal fear, *déjà vu* phenomena, and so on. These symptoms can be more distressing than the complete oblivion of grand mal. In this survey no direct question was asked on the record card for observers to indicate the patients who suffered from both kinds of attack, but many doctors did in fact record such cases. The incidence varied between the wide extremes of 0 and 80%. A high proportion of practices recorded no incidence of dual attacks, and this suggests that the occurrence of other forms of epilepsy in major epileptics is not fully recognized.

In no less than 18% of the practices no first fits were observed over the survey year. Thus in a population at risk of 60,000 no first fits were recorded where one would, on the average of the other practices, have expected to find 45 cases. One may conclude that some first fits were missed, possibly because the parents never sought the doctor's help.

From the annual rates of occurrence of first fits per 1,000 patients alive, by sex and age-groups as given in Table V, it is possible to make an estimate of the number of persons in a community who are likely to have a fit of some sort during their lifetime. By recourse to the Registrar-General's Life Tables (1951) we may estimate the numbers of persons out of a cohort of 1,000 births who are likely to be at risk in each age-group used in Table V. Then, on the assumption that the annual rates of first fits derived for the year of the survey are applicable in future years, we may calculate the expected number of first fits referable to each age-interval. The results of these calculations, for males and females combined, are given in Table XIII.

Thus just over 4% of all persons are likely to have a fit some time during life. This figure will be minimal, as the figures for first fits may be on the low side. A value of 5% will probably be near the truth, which agrees fairly well with the 6% quoted by W.H.O. (1957).

TABLE XIII.—*Expectation Throughout Life of the Occurrence of First Fits in a Cohort of* 1,000 *Births (Males and Females Combined)*

Age Interval	Expected No. Alive Out of 1,000 Births, at Midpoint of Interval	Rate of First Fits per 1,000 Alive, per Annum	Expected No. of First Fits during Interval
0–4	971·5	3·46	16·81
5–9	964·5	0·58	2·80
10–14	962·2	0·58	2·79
15–24	957·0	0·84	8·04
25–34	945·5	0·23	2·17
35–44	927·9	0·29	2·69
45–64	840·9	0·27	4·54
65–84	442·1	0·34	3·01
			42·85

Some persons who have a first fit will have no further attacks; others will go on to become chronic epileptics, and there will be an intermediate group. Table I shows that 0.42% of the population surveyed were chronic epileptics. It is possible to calculate roughly how many persons in such a population may be expected to have had a first fit, if the annual rates of occurrence of first fits found during the year of the survey are assumed to be applicable during previous years. We first construct a hypothetical population of 100,000 persons having the same age-structure as that surveyed. To the number of persons in a given age-group we apply the annual rate of occurrence of first fits for that age-group, multiplying by the length of that age-interval, and accumulate the corresponding products for previous age-groups to give the expected number of first fits for that age-group.

For example, the number of persons in the age-group 15–24 years is calculated to be 12,320. These persons are subject to the annual rates of first fits referable to age-groups 0–4, 5–9, and 10–14, for five years in each, and to the rate for the 15–24 age-group for half that interval. Thus it is estimated that 340 of the 12,320 persons in this age-group could be expected to have had a fit at some time during their lives.

If this method is applied to all age-groups it is estimated that about 3,200 of the population of 100,000 could be expected to have had a fit at some time, on the assumption that the persons in the various age-groups were subject to the annual rates of first fits throughout their lives. Thus 32 persons per 1,000 may be expected to have had a chance of being classed as a chronic epileptic, whereas the actual finding was 4.2. Hence the chances of a first fit being repeated at intervals and requiring continuous treatment are about one in eight.

This argument can be carried one stage further. Table VII shows that 74 persons in the series were totally disabled from work because of epilepsy and its consequences—that is, 20 per 100,000 of the population at risk. From this it can be deduced that one in every 160 persons (3,200÷20) having had a first fit will be severely disabled by chronic epilepsy. It is not a good thing to quote figures and statistics to patients or their relatives, but it is advisable for the doctor who is assessing the case to know roughly what are the chances of the fits recurring or becoming a serious affliction to the patient.

The problems and pitfalls of an investigation such as this are well known. The W.H.O. (1957) summarized the situation as follows: "Accurate statistics are notoriously difficult to obtain, especially in a disorder such as epilepsy, that is so often hushed up and that may only appear for a short time in a person's life." In this extensive survey of the epilepsies, carried out in some 67 general practices up and down England and Wales, an attempt has been made to circumvent some of these difficulties and to produce reliable figures of prevalence for the disease.

Summary

The findings of the survey suggest that between 4 and 5 persons per 1,000 in England and Wales were suffering from epilepsy. Grand mal was rather more common in males than in females, but with other forms of epilepsy the reverse was the case.

Epilepsy was most common between the years 15 and 24. First fits were most common in the first two years of life. Probably about 5% of persons have a fit of

some sort during their lifetime. Approximately one person in eight having a fit will go on to become a chronic epileptic, and about one in every 160 will become completely disabled by the disease.

Some 74% of all chronic epileptics were fully employed, 12% were in sheltered employment, 6% were unemployed for reasons other than epilepsy, and 8% were unemployed because of their fits or because of social difficulties arising from epilepsy. Some 3.5% of the patients received treatment of some sort in hospitals during the survey year. 16% of the cases presented a social problem. Fits were completely controlled in 42% of cases. A similar proportion had more than one fit in the year.

Phenobarbitone was the anticonvulsant most often used, with phenytoin sodium next and methoin third.

Consultants probably did not see more than 75% of the epileptics in the community, and an even smaller proportion of first fits.

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EFFECTS OF BRETYLIUM TOSYLATE ON BLOOD-PRESSURE, CARDIAC OUTPUT, AND RENAL FUNCTION IN HYPERTENSION

BY

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Although there is general agreement that ganglion-blocking drugs produce clinical improvement in hypertensive patients, their effective use may be limited by the occurrence of side-effects due to block of the parasympathetic ganglia. The severity and frequency of such side-effects have been diminished by combining other hypotensive drugs with smaller doses of ganglion-blocking drugs, but in spite of such measures, some patients have side-effects which are at best a nuisance and at worst may be intolerable. While such patients are now comparatively few, the report of Boura *et al.* (1959) that a new type of hypotensive agent, bretylium tosylate ("darenthin"), produced no block of the parasympathetic system suggested that this substance might prove to be better tolerated by many hypertensive patients.

We report here the effects of bretylium tosylate in 25 hypertensive patients treated for periods of up to nine months, and some observations on its effects on the cardiac output and renal function.

Methods

Clinical Observations

The 25 patients selected for treatment had been attending the hypertensive clinic at the Royal Melbourne Hospital, and had experienced troublesome side-effects while taking mecamylamine or pempidine. Most had also been taking 0.5 g. of chlorothiazide and 0.25 mg. of reserpine twice daily.

Initially the patients attended daily. The first oral dose of bretylium tosylate was 200 mg. twice daily; subsequently this was increased by increments of 100 mg. until a dose was reached which reduced the systolic blood-pressure to about 140 mm. Hg, with the patient standing. The blood-pressure was recorded at frequent

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intervals for seven hours, both in the supine and in the standing positions. Subsequently the patients were seen at regular frequent intervals in the hypertensive clinic.

Cardiac Output

In seven patients the cardiac output was measured by the dye-dilution method, using continuous sampling from an intra-arterial Cournand needle. Weighed samples of 2.5% solutions of cardiogreen (" indocyanine green ") were injected into the right median basilic vein, and arterial blood was collected through a photo-electric cuvette in two timed samples, the first before and the second during passage of the dye. The current from the cuvette was amplified and recorded. The blood concentrations of cardiogreen were estimated by the following technique: 1 ml. of the stirred blood sample was added to 0.5 ml. of 12.5% saponin, and 3 ml. of distilled water was then added; after shaking, the mixture was centrifuged for 10 minutes and the concentration of dye measured in a Unicam S.P. 600 spectrophotometer at a wavelength of 800 Å. Calibration curves were obtained by measuring the absorption of known concentrations of dye in the blood. Each dye-dilution curve was then calibrated by comparing the dye concentration of the appropriate blood sample with the mean deflection during the period of collection (McNeely and Gravallese, 1954), and the cardiac output was derived from the whole dye curve by the method of Hamilton *et al.* (1932).

Blood-pressure was recorded continuously except during the measurements of cardiac output, by connecting the arterial needle to a Sanborn electromanometer through a three-way tap. Before and after each measurement of cardiac output, the mean blood-pressure was recorded by electrical damping, to permit calculation of total peripheral resistance (T.P.R.).

Measurements were made with the patient resting on a tilting couch at a room temperature of 70° F. (21.1° C.). After the needles had been inserted the patient was allowed to rest for 10 minutes. A sham cardiac output was then performed, using saline instead of indicator. Measurements of cardiac output and blood-pressure were obtained with the patient supine and again after being tilted 60 degrees, feet down.

Bretylium tosylate, 50–150 mg., was injected intravenously over a period of three to five minutes. The patient then rested quietly, the blood-pressure being recorded continuously for 40–60 minutes or until a significant fall had occurred. Measurements of cardiac output and blood-pressure were then repeated in both postures.

Renal Function

This was estimated by measuring the clearance of sucrose (Steinitz, 1940), creatinine, and para-aminohippuric acid (P.A.H.). Five patients with severe hypertension were studied.

Observations were made with the patient in a cardiac bed, with the feet down, to avoid postural variations. All studies were carried out with the patient fasting. Loading doses of 4 ml. of a 20% solution of P.A.H. and 20 ml. of a 50% solution of sucrose were given intravenously, and an intravenous infusion containing 16 ml. of 20% P.A.H. and 50 ml. of 50% sucrose in 500 ml. of saline was then begun. 500 ml. of this solution was infused in five hours.

Samples of venous blood were taken during each clearance period from a thin-walled 18-gauge B.D. needle, left *in situ* in the other arm. Urine samples were obtained with an indwelling catheter.

The first clearance period began 90 minutes after the loading dose. Clearances were then measured in a 30-minute control period. 75 mg. of bretylium tosylate was given intravenously, and clearances were measured one hour, two hours, two and a half hours, and three hours afterwards. Blood-pressure was recorded at intervals by the auscultatory method. Blood and urine levels of sucrose, creatinine, and P.A.H. were estimated in duplicate.

Results

All but four of the 25 patients selected for trials with bretylium tosylate had previously been treated with mecamylamine or pempidine, and with chlorothiazide and reserpine, and had experienced parasympathetic side-effects of moderate or severe degree. In 10 the side-effects had not been severe enough to make control of the blood-pressure difficult, but in 11 the severity of side-effects had prevented fully effective doses being used. In addition, four previously untreated patients were given bretylium tosylate.

In all 25 the initial dose used was 200 mg. thrice daily. The dose ultimately required to achieve a therapeutically satisfactory fall of blood-pressure varied from 200 to 1,200 mg. t.d.s. The average dose required was 600 mg. t.d.s. In four patients, after an initial response had occurred, tolerance appeared to develop. In these the initially effective dose had to be doubled in three and increased threefold in one. In the remainder of the patients little or no tolerance was noted.

Effect on Blood-pressure

The blood-pressure rarely began to fall for two hours after an oral dose, and even with intravenous administration no effect was demonstrable before 30–60 minutes. The fall in blood-pressure reached a maximum at about three to five hours after an oral dose and had usually disappeared within six to eight hours. The postural fall of blood-pressure after bretylium tosylate was very conspicuous, often more so than when mecamylamine or pempidine was used; there was usually little or no fall of blood-pressure when the patient was supine, certainly in doses which were therapeutically tolerable. The concurrent use of chlorothiazide and reserpine often reduced the supine blood-pressure.

Unlike mecamylamine and pempidine, bretylium tosylate appeared to be only partly absorbed from the gastro-intestinal tract, for the effective intravenous dose was from one-fifth to one-tenth of the effective oral dose. Presumably because of variation in absorption, the effects on the blood-pressure varied somewhat from day to day. To some extent the variation in response could be reduced by the dose being taken before rather than after food, but even when this was done the effects were less predictable than the effects of mecamylamine or pempidine. Variation in response from day to day makes control of the blood-pressure difficult to achieve, as patients may experience episodes of hypotension and hypertension. Moreover, casual blood-pressures at clinic attendances tend to be higher in patients taking bretylium tosylate than in those taking mecamylamine or pempidine, which adds to the difficulty of management.

In all, the blood-pressure has been reduced to a moderately satisfactory degree in 19, but in six the control has been distinctly poor.

Side-effects

Side-effects due to parasympathetic blockade have not been reported by patients taking bretylium tosylate. In particular, patients who had previously had impotence, urinary retention, and severe constipation all claimed relief from these symptoms. However, side-effects attributable to sympathetic block have been noted. Bilateral Horner's syndrome and nasal stuffiness often occurred during the initial day or two of treatment, but have not persisted.

Bretylium tosylate seems to give rise to a group of side-effects apparently unrelated to autonomic block. The most conspicuous symptom has been pain in the region of the parotid glands, not usually accompanied by any swelling or by disturbance of salivation. The glands were often tender. This symptom was reported by 11 patients. Other symptoms included tremor in two, and mental depression, ceasing with withdrawal of bretylium tosylate, in the same two. Headache not apparently related to the height of the blood-pressure occurred in four. Two patients have discontinued bretylium tosylate because of the side-effects, preferring the discomforts of parasympathetic blockade.

General Assessment

Of the 25 patients treated two have died, both of cerebral haemorrhage. While their death cannot be confidently attributed to the change to bretylium tosylate, they were not as well controlled as when they were taking pempidine. Of the remaining 23, 11 have moderately well controlled blood-pressures with few or no side-effects. Six of the remainder have side-effects of moderate severity but prefer bretylium tosylate to other drugs. In most of them the main symptomatic improvement is relief of impotence. Bretylium tosylate was stopped in two because of the side-effects, and in the remaining four because ganglion-blocking drugs gave a much better control of blood-pressure.

Acute Circulatory Effects

Seven patients were studied. The results are shown in Table I. In six the mean blood-pressure fell by 15–51 mm. Hg in the horizontal position after bretylium tosylate, there being no change in the seventh. Further falls of blood-pressure occurred in all of the six patients who were tilted after taking the drug: this contrasts with the effects of tilting before taking it, when the mean blood-pressure rose in all seven patients.

In the horizontal position the cardiac output fell after bretylium tosylate in three patients, rose in two, and was substantially unaltered in two. The calculated T.P.R. fell in three, rose in one, and was unchanged in three.

On tilting before bretylium tosylate the cardiac output fell in all but one. After the drug the cardiac output fell on tilting in all six patients studied. In four the output was lower after bretylium tosylate than before, in one it was higher, and in one the same.

Before bretylium tosylate, the T.P.R. rose substantially on tilting in three. After bretylium tosylate it was substantially unaltered in the six patients studied.

It thus appears that bretylium tosylate produces falls of blood-pressure in the horizontal position which are the result primarily of a fall in cardiac output, with variable small changes in T.P.R. On tilting, the usual fall in cardiac output occurs, often to a greater degree and usually without the compensatory vasoconstriction which ordinarily occurs.

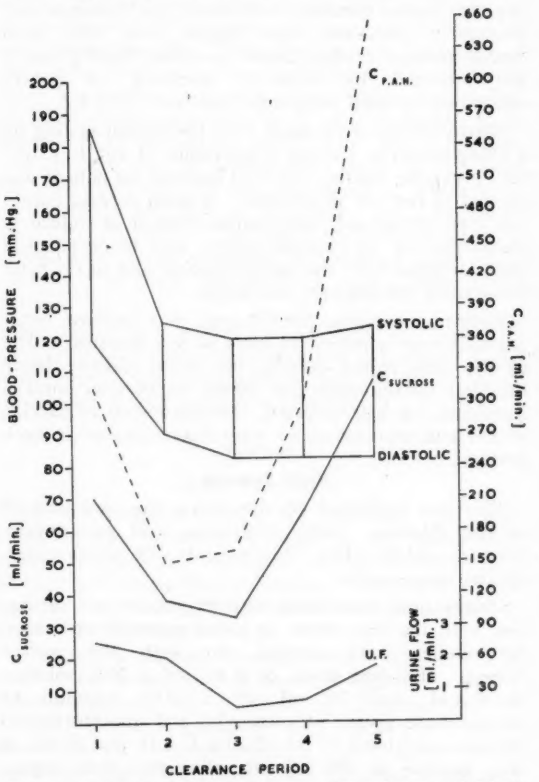
TABLE I.—*Changes in Mean Arterial Pressure, Cardiac Output, and Peripheral Resistance Induced by an Intravenous Dose of Bretylium Tosylate*

Patient	I.V. Bretylium Tosylate mg.	Posture	Mean Arterial Pressure (mm. Hg)		Cardiac Output (litres per min.)		Peripheral Resistance*	
			Before	After	Before	After	Before	After
			Bretylium Tosylate		Bretylium Tosylate		Bretylium Tosylate	
A	125	Supine	160	145	7·07	5·97	22·6	24·3
		60° tilt	169	134	6·14	4·62	27·5	29·0
B	150	Supine	130	130	6·49	6·97	20·0	18·7
		60° tilt	135	97	5·95	4·79	22·7	20·3
C	100	Supine	155	130	6·92	7·79	22·4	16·7
		60° tilt	165	60	4·66	4·07	35·4	14·7
D	125	Supine	170	119	8·71	5·37	19·5	22·2
		60° tilt	186	—	7·87		23·6	—
E	75	Supine	164	144	7·66	7·84	21·4	18·4
		60° tilt	172	122	4·61	6·82	37·3	17·9
F	50	Supine	165	130	6·24	4·61	26·4	28·2
		60° tilt	172	90	2·61	2·70	65·9	33·3
G	50	Supine	155	125	5·83	6·59	26·6	19·0
			170	85	6·86	4·07	24·8	20·9

* Calculated thus: $\frac{\text{Mean arterial pressure (mm. Hg)}}{\text{Cardiac output (litres per min.)}}$ and expressed in arbitrary units.

Effects on Renal Function

The responses in the five severely hypertensive patients studied were very similar. The reductions of blood-pressure and changes in urine volume and clearances are shown in Table II. It is evident that while the blood-pressure was falling both the glomerular filtration rate (G.F.R.) and the effective renal plasma flow



The mean changes in Csuc. CP.A.H., urine volume, and blood-pressure in five hypertensive subjects after an intravenous dose of bretylium tosylate. Clearance periods are those detailed in Table II.

TABLE II.—*Changes in Renal Clearance Values and Blood-pressure in Five Hypertensive Subjects. Period 1 is the Control Period Before, Period 2 One Hour, Period 3 Two Hours, Period 4 Two and a Half Hours, and Period 5 Three Hours After*

Observation	Subject 1. F. aged 45					Subject 2. F. aged 57					Subject 3. F. aged 53					Subject 4. M. aged 46					Subject 5. M. aged 50				
	Period					Period					Period					Period					Period				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Blood-pressure mm.Hg	170/130	145/105	120/90	130/90	130/90	185/120	130/100	130/90	130/90	140/80	180/110	90/60	110/80	100/70	100/80	190/120	155/105	130/90	130/90	125/90	200/120	100/60	110/60	110/70	110/70
$C_{suc.}$ ml./min. ..	63	49	27	73	84	92	53	27	39	140	42	15	22	75	123	74	36	66	78	77	81	19	18	—	50
$C_{P.A.H.}$ ml./min.	209	173	108	266	380	396	203	135	115	770	153	88	153	463	670	368	151	309	373	396	434	128	112	—	1160
C_{CR} ml./min. ..	96	60	39	122	127	86	65	8	32	170	47	3	—	89	150	93	62	88	98	146	126	27	23	—	250
U/P% suc. ..	11	11·5	64	86	84	13	19	89	85	80	8	15	22	73	91	58	62	83	113	105	10	11	23	—	
UV ml./min. ..	2·75	4·17	0·25	0·57	0·35	2·84	2·34	0·21	0·20	1·17	3·46	0·05		0·04	1·86	0·80	0·80	0·80	0·47	0·71	2·9	2·0	0·76	—	4·0

U/P = Urinary concentration/plasma concentration. UV = Urinary volume.

(E.R.P.F.) fell to between 25% and 60% of the control levels. However, although the blood-pressure remained low two and a half hours and three hours after the injection, the G.F.R. and E.R.P.F. had risen to values well above the initial levels. The urinary volume fell sharply as the blood-pressure fell and usually remained low for the remainder of the experiment, with a resulting rise in the U/P ratio. The mean changes are shown in the Chart.

Discussion

In the past 10 years the means available for treating high blood-pressure have progressed from the intermittent hypotensive effects of parenterally administered hexamethonium to the very effective combination of chlorothiazide, reserpine, and mecamylamine or pempidine. With a combination of the latter drugs for the treatment of 70 severely hypertensive patients in the hypertensive clinic excellent control of blood-pressure has been achieved with few or no side-effects in 49 out of 70 patients. In 10 of the remainder side-effects were only moderately severe, but in 11 they were severe enough to cause difficulty in management.

Thus in 21 of the 70 there was reason for attempting to improve the existing regime. In all but two of them side-effects have almost completely disappeared with bretylium tosylate, but in almost all the degree of control of blood-pressure is not as good with bretylium tosylate as in those still taking ganglion-blocking drugs. For this reason we still regard mecamylamine or pempidine rather than bretylium tosylate as the drug of choice in the treatment of severe hypertension. All are best used in combination with chlorothiazide and reserpine. When parasympathetic side-effects cause symptoms, bretylium tosylate seems to be a useful alternative to mecamylamine; in young men who are likely to experience impotence bretylium tosylate is the drug of choice. In some patients control of blood-pressure may be improved without severe side-effects by using bretylium tosylate, chlorothiazide, and reserpine, with a small dose of mecamylamine.

From our observations of the acute effects of bretylium tosylate on cardiac output it seems that this drug, like the ganglion-blocking drugs, prevents compensatory vasoconstriction in the erect posture and may have little effect on the total peripheral resistance or blood-pressure when the patient is supine. Indeed, when the supine blood-pressure is reduced it seems to be usually the result of a fall in cardiac output, although occasionally a small fall in total peripheral resistance may occur.

However, the effects of bretylium tosylate on renal function and blood flow seem to differ from those of other hypotensive drugs, for though both the G.F.R. and the E.R.P.F. fall when the blood-pressure falls, both recover and usually exceed the resting levels, even though the blood-pressure remains low. Reports of the effects of ganglion-blocking drugs have all shown that the G.F.R. and E.R.P.F. fall in proportion to the fall in blood-pressure (Mills and Moyer, 1953; Hershberger, 1955); while these values may sometimes return towards normal when the blood-pressure is still low, no reports of a rise in G.F.R. and E.R.P.F. occurring during the hypotensive phase seem to have been made. The only drug which has been reported to raise the E.R.P.F. is hydrallazine, but with this drug the G.F.R. remains low (Mackinnon, 1952). It seems from this unique action that bretylium tosylate may be worthy of trial in patients with severe hypertension and diminished renal function.

Summary

Bretylium tosylate, a new hypotensive drug, enables the blood-pressure to be reduced with no parasympathetic side-effects, but the falls in blood-pressure produced are less predictable than those produced by mecamylamine.

For most patients with severe hypertension the treatment of choice is chlorothiazide and reserpine, with mecamylamine. When side-effects of the latter are severe bretylium tosylate should be used.

The acute effects of bretylium tosylate on the circulation have been studied. A fall in cardiac output occurs as the blood-pressure falls, with an absence of compensating vasoconstriction.

Though bretylium tosylate produces a transient fall in renal clearance values, these usually rise subsequently to levels greater than the control values although the hypotensive effect persists.

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TREATMENT OF CHORIOCARCINOMA WITH A COMBINATION OF CYTOTOXIC DRUGS

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It is known that both normal embryonic development in the rat and growth of the female genital tract are dependent upon the availability of folic acid (Nelson and Evans, 1949; Hertz and Tullner, 1949). It was therefore postulated by Hertz and his colleagues (Li *et al.*, 1956; Hertz *et al.*, 1958) that trophoblastic tumours originating in the foetal chorion might prove sensitive to folic-acid antagonists. These workers introduced the administration of anti-folic-acid therapy to patients with malignant trophoblastic tumours and reported five complete remissions and 17 partial remissions in a series of 27 cases. Resistance to folic-acid antagonists appeared to develop during therapy in some of their patients.

By crude analogy with the antibiotics, it seemed likely that resistance to cytotoxic substances, especially those with an antimetabolite action, would develop less readily when used in combination. There is also some experimental evidence which suggests that combinations of cytotoxic drugs may be more effective than the same drugs used alone (Skipper *et al.*, 1954). Augmented toxic effects on normal tissues would also be expected.

The use of a combination of drugs administered concurrently in the treatment of two cases of pulmonary hypertension due to trophoblastic tumours was described briefly by Bagshawe and Brooks (1959). The present paper describes the results of combined cytotoxic therapy in six patients who had chorionic growths. Clearly the use of such combinations of drugs is largely empirical, and much work will be required to find the best combinations. The drugs chosen in the first stage of this study were the folic-acid antagonist methotrexate (4-amino-N^{10}-methylpteroylglutamic acid), which blocks the conversion of folic to folinic acid, and 6-mercaptopurine. The latter drug has also been shown to exert a severe toxic effect on foetal tissues and acts as an antagonist of hypoxanthine and adenine. It was also decided that, should resistance to this combination of drugs develop, then a drug of the nitrogen-mustard group, such as chlorambucil, would be employed in place of the 6-mercaptopurine.

Methods

Diagnosis was established by histological examination or by the clinical and radiological findings in conjunction with elevated gonadotrophin excretion. The well-known difficulties in the histological diagnosis of choriocarcinoma are not considered here, since all six cases had evidence of multiple metastases.

The urinary gonadotrophin excretion was assayed in terms of the effect upon mouse uterine weight (Klinefelter *et al.*, 1943; Loraine and Brown, 1954). This bioassay is of a semi-quantitative nature, but was adequate for the measurement of the major changes observed in the present series. The values obtained in this laboratory in non-pregnant pre-menopausal women are below 100 mouse units/day, and in post-menopausal or oophorectomized women the values are usually in the range 200–400 mouse units/day.

Recently these results have been supplemented by estimations of human chorionic gonadotrophin in terms of international units, but the results are not included in this communication. A modification of the method of Loraine (1950) was employed, and details of this and other aspects of the biological assays will be published later.

Surgical Treatment.—In the present series of cases hysterectomy and bilateral oophorectomy had been performed on two patients before starting cytotoxic therapy. One patient had hysterectomy and unilateral oophorectomy and one had hysterectomy alone. Two cases had no surgical treatment.

Radiotherapy.—Case 3 had *x*-ray therapy to the eyes before cytotoxic treatment was started.

Drug Treatment.—Methotrexate and 6-mercaptopurine were given concurrently in divided doses for courses of three to five days. The patients received between 4 and 12 such courses. The usual dose of methotrexate was 25 mg. a day in divided doses by mouth, and 6-mercaptopurine was given in doses of 600 mg. daily by the same route. Both doses are grossly in excess of those in common use. A five-day course of treatment was given unless there were residual effects from previous treatment. Antibiotic cover was given during and after each course of treatment, and was continued until the white-cell count had returned to normal. Chlorambucil was given in doses of 10 mg. daily for 6- or 10-day courses, and methotrexate was given during the last three to five days of each course of chlorambucil. The interval between courses was kept as short as was compatible with reasonable safety. The chief limiting factors in this were stomatitis and the peripheral blood picture. The gonadotrophin excretion fell after each course but increased rapidly again if further treatment were delayed, and this rise probably indicated a recurrence of tumour growth. It was sometimes necessary, therefore, to give a further course of therapy even though the total leucocyte count was still depressed. Such courses were usually of only three days' duration, but, even so, they were often followed by severe toxic reactions. It was found essential to base the timing and duration of each course of treatment on frequent, sometimes hourly, assessments of the patient's condition. Such assessments were made difficult by the fact that the toxic effects were maximal several days after completion of each course.

Terminal Phase of Treatment.—Treatment was continued at the maximum intensity which the patient could tolerate until the gonadotrophin titre had been within the normal range for a period of 6 to 10 weeks, and only when this was achieved have we considered the patient to be in a state of hormonal remission.

Case Histories

The clinical features and initial response to treatment in Case 1 were described in a previous paper (Bagshawe and Brooks, 1959), and Case 2 was described in an addendum to the same paper. The main features of all six cases are summarized in Tables I and II.

TABLE I

Case No.	Age	Pelvic Findings	Pulmonary Metastases	Other Metastases	Surgical Treatment	General Condition at Start of Cytotoxic Therapy
1	30	Nil diagnostic	Multiple embolism and pulmonary hypertension	None found	Hysterectomy; unilateral oophorectomy	Gross dyspnoea and anoxaemia
2	28	,, ,,	Severe pulmonary hypertension	,, ,,	Nil	Severe exertional dyspnoea
3	24	7 cm. diameter uterine tumour, choriocarcinoma	Several small metastases on *x*-ray film	Bilateral retinal deposits	Hysterectomy and oophorectomy	Wasted. Severe bilateral impairment of vision
4	24	5 cm. diameter uterine tumour, choriocarcinoma	Multiple metastases	Abdominal glands	,, ,,	Fair
5	23	Mass in right foraix. Curettings—choriocarcinoma	,, ,,	Vagina	Nil	,,
6	31	Malignant mole, 1954	One large, several smaller metastases	Epidural and intracranial	Hysterectomy	Staphylococcal pneumonia. Cauda equina lesion, urinary incontinence, and infection

TABLE II

Case No.	Treatment		Total Dosage			Gonadotrophin Titre M.U.U.		Duration of Remission in Months	Other Features
	No. of Courses	Duration (Months)	Methotrexate (mg.)	6-Mercaptopurine (g.)	Chlorambucil (mg.)	At Onset of Treatment	May, 1960		
1	10	7	1,200	28·8	—	300,000	25	19	Complete remission
2	7	6	725	17·4	—	50,000	75	18	Persistent pulmonary hypertension
3	12	6½	1,250	30·0	—	4,500	150	6	Complete remission. Only slight impairment visual acuity
4	14	9	975	32·2	300	2,000,000	200	2	Marked bone marrow depression during treatment. Complete remission
5	5	5	650	—	—	650,000	25	6	Complete remission. Normal menstruation
6	4		500	11·5	—	?	100	—	Died after 4 courses of treatment. Pyelonephritis. Necrotic cerebral and pulmonary tumours

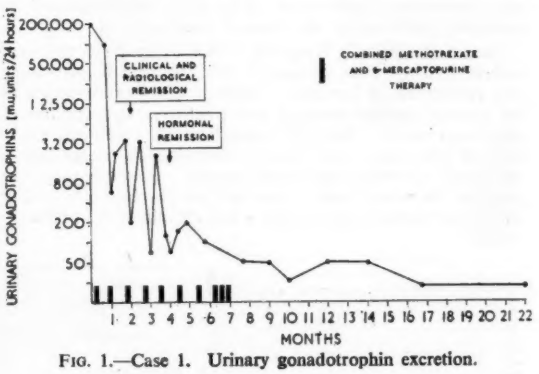

FIG. 1.—Case 1. Urinary gonadotrophin excretion.

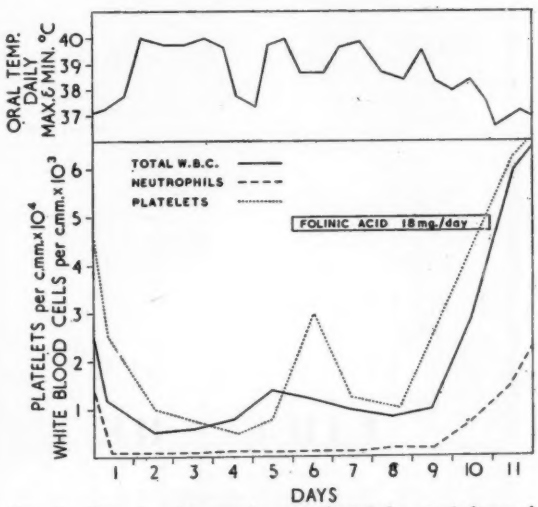

FIG. 2.—Case 1. Leucopenia complicated by staphylococcal infections after tenth treatment.

Case 1 (St. Mary's Hospital).—This patient had recurrent pulmonary embolism leading to severe pulmonary hypertension. Hysterectomy for menorrhagia failed to provide the diagnosis, but this was made subsequently on the basis of raised gonadotrophin excretion. At the time treatment started the patient was severely dyspnoeic at rest. Though severe toxic effects followed the first course of therapy, the improvement in her respiratory function was rapid enough to allow her to leave hospital temporarily only two weeks after the start of treatment. A total of 10 courses of treatment was given during a period of six months (Fig. 1). After the final course of treatment severe leucopenia developed and was complicated by numerous staphylococcal lesions in the skin and lungs. Haematopoietic recovery followed treatment with fresh blood transfusions and folinic acid (Fig. 2). The pulmonary-artery pressure and electrocardiogram have reverted to normal, and complete clinical, radiological, and hormonal remission has persisted since November, 1958. (Time of reporting May, 1960.)

Case 2 (Radcliffe Infirmary and St. Mary's Hospital).—This 28-year-old woman presented with pulmonary hypertension which had first caused symptoms three months after a normal full-term delivery. Diagnosis was established by gonadotrophin assay. Seven courses of treatment were given, and complete hormonal remission has persisted since November, 1958. Marked improvement in exercise tolerance was noted during therapy, and it seemed probable that the pulmonary hypertension had lessened. Cardiac catheterization after completion of therapy showed, however, that, though there had been an appreciable fall in the pulmonary vascular resistance, the pulmonary-artery pressure was grossly unchanged. After discharge from hospital the improved exercise tolerance persisted for four months but then deteriorated. This patient appears to have developed an irreversible pulmonary hypertension.

Case 3 (Mount Vernon Hospital and St. Mary's Hospital). This 24-year-old woman presented with menorrhagia after a normal full-term pregnancy. She then developed frontal headaches and bilateral retinal detachments with retinal metastases. Her vision was severely impaired and she lost weight. Diagnostic curettage established a diagnosis of choriocarcinoma, at which time metastases became apparent on the chest *x*-ray film (Fig. 3). The Hogben test was negative throughout the illness, and the gonadotrophin

assay, though raised, never reached the levels usually associated with chorionic tumours. Hysterectomy revealed a rounded 7-cm. choriocarcinoma in the uterus. Radiotherapy was given to the eyes, and cytotoxic therapy was started subsequently. Though the chest *x*-ray film was clear after six weeks of cytotoxic therapy, hormonal remission was achieved only after five months. There was a progressive improvement in visual acuity, and at the completion of therapy this was assessed at approximately 6/12 in both eyes with small residual field defects.

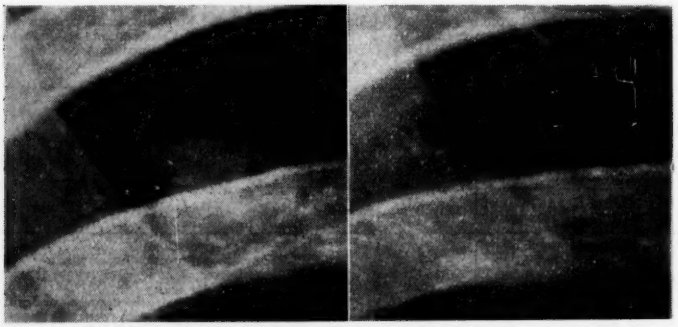

FIG. 3.—Case 3. Left: Part of chest *x*-ray film taken on June 17, 1959, showing pulmonary metastasis. Right: *x*-ray film of same part of chest taken on August 8.

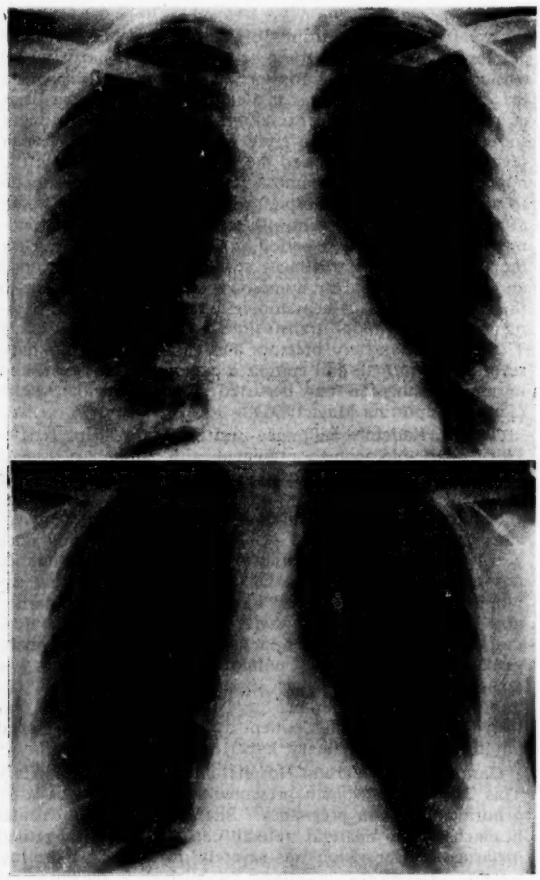

FIG. 4.—Case 4. Top: Chest *x*-ray film taken on July 30, 1959, showing multiple small metastases in both lung fields. Bottom: Chest *x*-ray film taken on September 10, showing radiological clearing after six weeks' treatment.

Case 4 (Paddington General Hospital).—This 24-year-old woman presented with menorrhagia after a normal full-term pregnancy. Diagnosis was made on examination of curettings, and at hysterectomy a 5-cm. diameter haemorrhagic tumour was found in the uterine wall. Pulmonary metastases appeared, but these resolved within six weeks of the start of therapy (Fig. 4). The fall in the gonadotrophin assay was erratic, and after five months' treatment chlorambucil was substituted for 6-mercaptopurine. Normal gonadotrophin levels were attained only after a total of eight months' treatment (Fig. 5). A tendency to prolonged bone-marrow depression contributed to the slow progress in this case. She was in complete remission at the time of reporting.

Case 5 (Luton and Dunstable Hospital).—This 23-year-old woman developed vaginal bleeding five weeks after a normal pregnancy. Examination two months later revealed a mass in the right fornix, and chest *x*-ray examination showed numerous metastases. Examination of uterine curettings confirmed the presence of choriocarcinoma. Methotrexate was started in three-day courses of 15 mg. a day. At first the metastases on the chest *x*-ray film appeared more numerous, and a vaginal metastasis developed. Treatment with only three courses of methotrexate in full dosage was followed by a remarkably rapid disappearance of the mass in the uterus and of the vaginal and pulmonary metastases (Fig. 6). She remained in complete remission at the time of reporting.

Case 6 (St. Mary's Hospital).—This 31-year-old coloured woman had a molar pregnancy in 1954, and hysterectomy was performed in Jamaica. Microscopical examination of the tumour showed areas of active infiltration suggestive of choriocarcinoma. After the operation she developed weakness of the legs and urinary incontinence, suggesting a metastasis involving the cauda equina. Radiotherapy was given to the lower back. Late in 1958 she began to feel ill and to lose weight, and a chest *x*-ray examination in Novem-

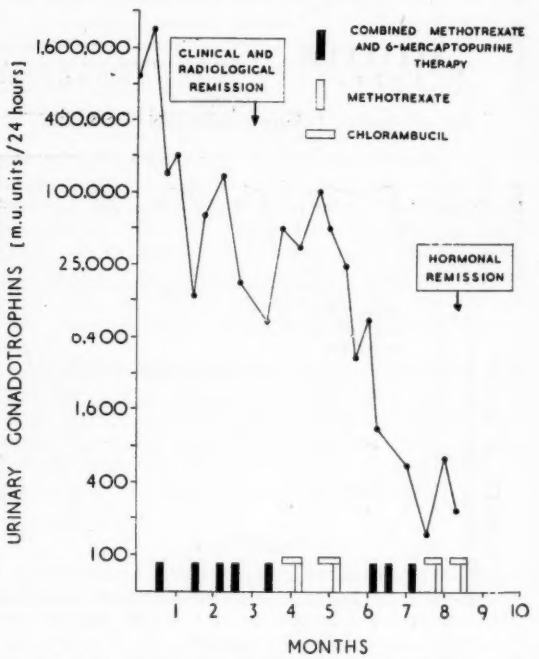

FIG. 5.—Case 4. Urinary gonadotrophin excretion.

ber, 1959, revealed a large well-defined shadow in the left lung field. On presentation for treatment she was severely anaemic and had a staphylococcal pneumonia in addition to a long-standing urinary infection. Methotrexate and 6-mercaptopurine were given under antibiotic cover, and severe intestinal bleeding followed. She became confused, and after the second course of treatment developed focal seizures. The third course of treatment consisted of a three-day course of intrathecal methotrexate, and she had no further fits until after the fourth course of treatment. Heavy sedation was then necessary to control the fits, and this coincided with the hepatic dysfunction which followed cytotoxic therapy. She died in coma 10 days after the end of the fourth treatment. Necropsy was performed by Dr. K. Porter, and revealed a necrotic mass in the left lung and two small necrotic cerebral metastases. On histological examination all recognizable tumour cells showed pyknosis and other degenerative changes. There was extensive renal infection and histological evidence of focal hepato-cellular damage.

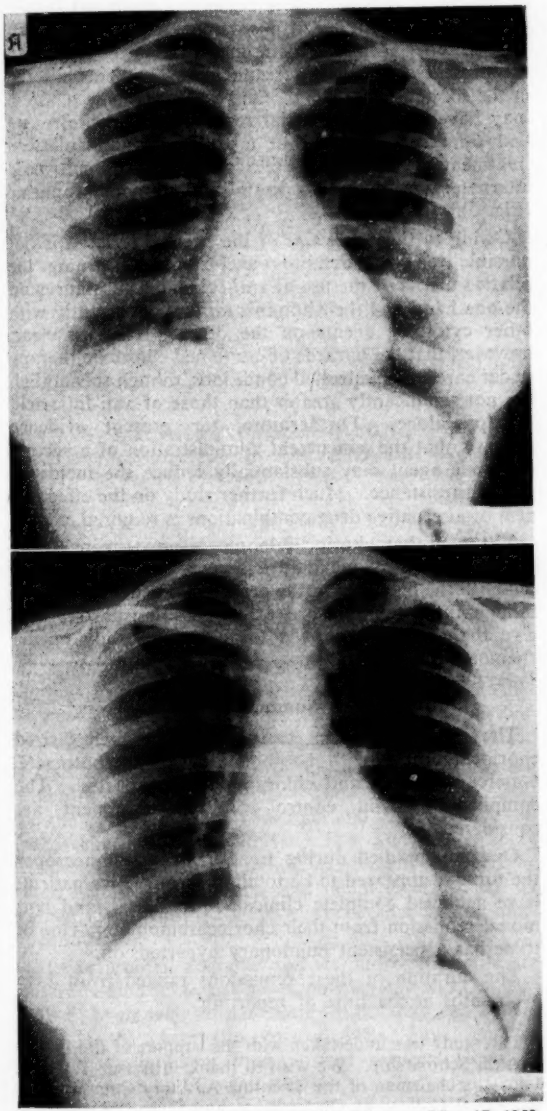

FIG. 6.—Case 5. Top: Chest *x*-ray film taken on May 17, 1959, showing multiple metastases in both lung fields. Bottom: Chest *x*-ray film taken on November 10, showing complete radiological resolution.

Side-effects of Treatment

Serious toxic effects are invariably encountered in the systemic administration of large doses of antimetabolite substances, and deaths have been attributed to intestinal, hepatic, and bone-marrow damage (Hertz *et al.*, 1958). The use of a combination of antimetabolite drugs in massive dosage might be expected to cause more severe toxic damage. Though side-effects in the present group were severe, they do not appear to have been appreciably worse than those encountered in the use of folic-acid antagonists alone. The one death in the present series could be partially attributed to the drugs aggravating a pre-existing renal infection and to impaired detoxication of anti-epileptic drugs.

The common side-effects were stomatitis, proctitis, nausea, vomiting, occasional diarrhoea, intestinal bleeding, jaundice, paronychial infections, blotchiness of the skin, pigmentation, diffuse alopecia, anaemia, leucopenia, thrombocytopenia, and proteinuria. Side-effects became apparent between the fourth and eighth days after the start of each course of treatment. They were maximal between the seventh and fourteenth days, and recovery from the acute effects was complete between the tenth and twentieth days.

Stomatitis proved to be the most trying symptom. Jaundice was transient, but gross temporary derangement of liver function was revealed by "bromsulphalein" excretion tests immediately after a course of treatment. Liver-function tests on completion of therapy have been normal. Proteinuria has been mild and usually occurred only after the initial courses of treatment. Detailed studies of renal function have not been performed, but blood-urea levels have remained normal throughout, except in Case 6, in which there was a long-standing urinary infection.

Haemoglobin levels during treatment were usually in the range of 7–11 g./100 ml., and progressive falls did not commonly occur. In Case 4 bone-marrow depression, especially with respect to the platelets, tended to be more severe and to persist longer after each course of treatment than in the other cases, and this has led to prolongation of treatment.

Alopecia progressed steadily throughout the first four to five months of treatment, though hair growth recurred before each course, and towards the end of treatment this appeared to proceed despite further cytotoxic therapy. After completion of therapy hair growth and texture returned to normal.

Control of Side-effects

A normal diet was given throughout, except when prohibited by stomatitis. No attempt was made to restrict or augment the folic-acid content of the diet. On some occasions parenteral fluid therapy was necessary.

Stomatitis was partially alleviated by a variety of local measures, but when it was severe intramuscular pethidine provided the only satisfactory relief. Latterly, a very weak solution of folinic acid was applied to the buccal mucosa during treatment, and this appeared to diminish the severity of the stomatitis. It is not yet certain whether such applications have an adverse effect on the course of treatment, but this seems improbable.

Specific therapy for bone-marrow depression was necessary on only two occasions, and consisted of

transfusions of fresh blood and folinic acid in doses of up to 18 mg. a day.

The risk of irreversible bone-marrow damage was always present during this form of treatment. Because of this risk, bone-marrow was aspirated from four of the patients and was cooled and stored at −78° C. by methods similar in principle to those described elsewhere (see, for example, Pegg and Trotman, 1959). The occasion to return stored marrow has not so far arisen in the patients under review, but it would seem to be unjustifiable not to make use of this potential safety factor in the event of a failure to respond to folinic acid. The fact that severe marrow depression after cytotoxic therapy may recover without marrow transfusions is illustrated by the events in Case 1 (Fig. 2); a similar sequence occurred in Case 5. Bone-marrow depression was not evident in Case 6 at the time of death.

The provision of wigs was of value in reducing mental depression and resistance to further therapy on account of alopecia.

General Discussion

The remissions from widespread malignant choriocarcinoma which have been achieved in five of these six cases and in some of the much larger group reported by Hertz *et al.* (1958) have probably been more profound than those seen in other forms of malignant disease treated by chemotherapeutic methods. While it is too early to regard these cases as cured, the possibility that this may have occurred in at least some instances cannot be dismissed. Moreover, it should be possible to detect hormonal evidence of recurrence of such tumours before there is any clinical or radiological evidence of their recurrence. The fact that two patients in this series received large amounts of folinic acid at the end of their treatment without evidence of relapse supports the view that any remaining tumour cells were not capable of active metabolism and division at that time. The administration of folinic acid after completion of therapy as a test for the presence of viable tumour cells suggests itself, but further experience will be required before this can be safely, or reliably, established.

The treatment of trophoblastic tumours with these agents may have some bearing on the treatment of other forms of malignant disease, and a quantitative guide to therapy such as the gonadotrophin assay emphasizes the insensitivity of clinical and radiological methods as such a guide. It is notable that though malignant trophoblastic tumours appear to be more sensitive to certain cytotoxic agents than many other tumours, the amount and duration of therapy necessary to achieve full remission is considerably greater than that usually employed in the chemotherapy of malignant disease.

It will be possible to define the place of surgical intervention in the treatment of choriocarcinoma only after much further experience has been gained with cytotoxic methods. Clearly, hysterectomy may have to be performed either to establish the diagnosis or to stop haemorrhage. Even when neither of these reasons applies it may be advisable to remove the uterus when it is the site of a large tumour, because the risk of haemorrhage seems to be greater when a large tumour is undergoing necrosis. Similarly, there may be a case for the removal of a large solitary pulmonary metastasis, especially if situated peripherally and if there is haemorrhage. However, Case 5 demonstrates that these complications are by no means inevitable even with large metastases. It may be significant, also, that the two patients who did not have hysterectomy and oophorectomy responded most readily to cytotoxic treatment. On the present evidence it seems that hysterectomy and oophorectomy should not be performed without adequate reason, even though the spontaneous disappearance of metastases has been reported on rare occasions after surgical removal of the primary tumour.

It is evident from the work of Hertz *et al.* (1958), Li (1959), and Douglas (1959) that complete hormonal remissions have been obtained in about 25% of patients with malignant trophoblastic tumours treated with folic-acid antagonists alone. In other cases initial sensitivity to folic-acid antagonists has been followed by partial or complete resistance. Where other forms of chemotherapy have been used subsequent to the development of resistance to folic-acid antagonists, continued failure to respond has suggested a crossover in tumour resistance to other forms of chemotherapy (Hertz, 1959). In the present series drug resistance was not encountered in the six patients treated. One of our patients (Case 4) may have developed partial resistance to methotrexate and 6-mercaptopurine, but a full remission followed treatment with methotrexate and chlorambucil used alternately with methotrexate and 6-mercaptopurine (Fig. 5).

Owing to the small size of the present series it is not possible to draw definite conclusions concerning the relative merits of the use of anti-folic-acid substances on the one hand and their administration concurrently with other cytotoxic agents on the other. It seems clear, however, that the hazards of combined cytotoxic therapy under carefully controlled conditions, though substantial, are not significantly greater than those of anti-folic-acid therapy alone. Furthermore, the present evidence suggests that the concurrent administration of a second cytotoxic agent may substantially reduce the incidence of drug resistance. Much further study on the effectiveness of alternative drug combinations is required.

The fact that choriocarcinoma is now amenable to cytotoxic therapy inevitably imposes an obligation to establish the diagnosis at the earliest moment. Moreover, though these tumours are rare, their unusual features give them an important position in the study of the chemotherapy of cancer.

Summary

The treatment of six cases of widely metastasized choriocarcinoma with combinations of methotrexate, 6-mercaptopurine, and chlorambucil is reported. The complications and control of this treatment are considered.

One patient died during treatment, and at necropsy the tumour appeared to be totally necrotic. Five patients have achieved complete clinical, radiological, and hormonal remission from their choriocarcinomata. One of these has a persistent pulmonary hypertension.

The duration of these remissions ranged from 2 to 19 months at the time of reporting.

This study was undertaken with the support of the Edgar-Gentilli Scholarship. We wish to thank Professor T. N. A. Jeffcoate, chairman of the Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists, for his generous help. We are indebted to Dr. Margaret I. Stern, Miss Joan Bonfield, and other members of the staff of the Endocrine Unit, Chelsea Hospital for Women, working

under the direction of Dr. Ian F. Sommerville, for their help with the gonadotrophin assays. We also thank Dr. W. D. W. Brooks, Mr. G. C. Brentnall, Dr. H. E. Edwards, Miss A. M. Fleming, Professor W. S. Peart, Professor Sir George W. Pickering, Mr. I. Spiro, and Dr. P. Strickland for permission to study their patients and publish case reports. We also thank the registrars, house staff, and nursing staff whose co-operation made this study possible.

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NUCLEAR SEX AND BODY-BUILD IN SCHIZOPHRENIA

BY

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A recent survey on body-build has shown that schizophrenics differ markedly from normal subjects with regard to the biacromial diameter and the androgyny score. Groups of patients of both sexes were found to have a much lower (more female) androgyny score and a smaller biacromial diameter than did groups of normal men and women (Rey and Coppen, 1959). The androgyny score is obtained by the formula :

$$3 \times \text{biacromial diameter (cm.)} - 1 \times \text{bi-iliac diameter (cm.)}.$$

The androgyny score for normal individuals has been shown to have a normal distribution for each sex, with a mean of 90.1 (S.D. 4.7) for men and of 78.9 (S.D. 4.6) for women (Tanner, 1951). The androgyny score enables effective discrimination to be made between the sexes. Out of 409 men and women examined by Tanner (1951) only 12% were misclassified on the basis of the androgyny score.

The biacromial diameter and the androgyny score are closely related to sexual development (Rey and Coppen, 1959). Moreover, it has been found that anatomical males with chromatin-positive cells have smaller biacromial diameters than normal subjects (Raboch, 1957 ; Coppen and Cowie, 1960).

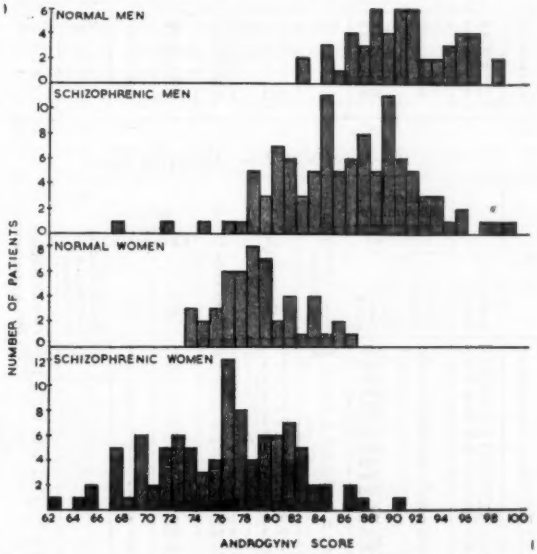
There are grounds for believing that some connexion may exist between anomalies of nuclear sex and mental disorders. Thus Pasqualini *et al.* (1957) described a number of individuals with Klinefelter's syndrome who showed hypokinesis and timidity from an early age. They were usually idle, slept too much, lacked vital interests, and were shy, restrained, and had few friends. They were of low intelligence with a mean I.Q. of 81. In line with this last observation Ferguson-Smith (1958, 1959) found that just over 1% of male patients in a mental deficiency hospital and 1.2% of educationally subnormal male children had chromatin-positive Klinefelter's syndrome. These percentages greatly exceed that of 0.26% reported by Moore (1959) in an unselected group of newborn male infants.

Taking all these facts into consideration, it is not unreasonable to suspect that there may be changes in nuclear sex associated with schizophrenia. However, as many schizophrenics have a normal physique and as the classification of schizophrenia may well include heterogeneous groups of patients, it seems likely that if anomalies of nuclear sex occurred in this condition they would be found in patients with a female type of body-build.

In the present investigation male schizophrenics with an androgyny score characteristic of normal women were selected from a schizophrenic population for the examination of nuclear sex. A similar examination was carried out with a group of female schizophrenics with significantly reduced androgyny scores, as it is known that women with gonadal dysgenesis frequently have anomalies of physique and often lack sex chromatin (Grumbach *et al.*, 1955).

The Investigation

We examined 100 male and 100 female mental hospital patients with a diagnosis of chronic schizophrenia. In every case the biacromial and bi-iliac diameters were measured with a Martin anthropometer. The androgyny scores for patients of both sexes are shown in the Chart. The mean androgyny scores for both the male and the female


NORMAL MEN
SCHIZOPHRENIC MEN
NORMAL WOMEN
SCHIZOPHRENIC WOMEN
NUMBER OF PATIENTS
62 64 66 68 70 72 74 76 78 80 82 84 86 88 90 92 94 96 98 100
ANDROGYNY SCORE

Distribution of androgyny score in schizophrenic patients and normal subjects.

*In receipt of a grant from the Medical Research Council.

groups were greatly reduced when compared with values obtained from groups of normal men and women. The mean androgyny score of the female schizophrenics was 76.1 (S.D. 5.5) and that of the male schizophrenics was 86.2 (S.D. 5.4). The figures obtained are in accordance with previous findings in the case of schizophrenic patients (Rey and Coppen, 1959).

From the total number of patients, three groups were selected on the basis of their androgyny scores. One group consisted of 6 male patients with an androgyny score of 89 or over, within the range for normal men. A second group of 16 men had androgyny scores less than 82, approximately the mean score for normal women. A third group consisted of 20 female patients whose androgyny score was under 72. Androgyny scores of this order are much lower than those found in normal women. It was thought that if any of the women lacked sex chromatin they would most likely be found in this group whose body-build showed the greatest deviation from normal.

A scraping of buccal mucosa and a smear of capillary blood from the ear were taken from each of the patients in these groups. Assessment of nuclear sex was carried out according to the method of Moore and Barr (1955) and Davidson and Smith (1954).

The results are set out in detail in Tables I–III. In spite of the wide deviation from normal of the androgyny scores, no anomalies of nuclear sex were discovered.

The estimation of androgyny scores was considered to be a good screening device for selecting patients likely to show inconsistencies between anatomical and chromosomal sex. It seems improbable, therefore, that nuclear-sex anomalies are associated in any significant degree with schizophrenia, or that they are responsible for the marked differences in body-build between schizophrenic patients and normal individuals.

TABLE I.—*Males with Normal Androgyny Score*

No.	Androgyny Score	Blood Chromatin: Observed: No. of Nodules	Blood Chromatin: Observed: No. of Neutrophils	Blood Chromatin Assessment	+Eosinophils	Mean Lobe Count	Buccal Mucosa Chromatin: % Neg.	Buccal Mucosa Chromatin: % Pos.	Buccal Mucosa Chromatin Assessment	Overall Nuclear Sex Assessment
1	90·5	0	500	Neg.	0: 10	3·37	98	2	Neg.	Neg.
2	89·6	0	500	,,	0: 37	2·97	97	3	,,	,,
3	91·4	0	500	,,	0: 10	3·06	99	1	,,	,,
4	95·3	0	500	,,	0: 7	2·89	97	3	,,	,,
5	91·6	0	500	,,	0: 16	3·29	97	3	,,	,,
6	97·5	0	500	,,	0: 2	3·11	98	2	,,	,,

TABLE II.—*Males with Low Androgyny Score*

No.	Androgyny Score	Blood Chromatin: Observed: No. of Nodules	Blood Chromatin: Observed: No. of Neutrophils	Blood Chromatin Assessment	+Eosinophils	Mean Lobe Count	Buccal Mucosa Chromatin: % Neg.	Buccal Mucosa Chromatin: % Pos.	Buccal Mucosa Chromatin Assessment	Overall Nuclear Sex Assessment
1	78·5	0	500	Neg.	0: 20	2·96	97	3	Neg.	Neg.
2	78·7	0	500	,,	0: 9	3·40	95	5	,,	,,
3	77·0	0	500	,,	0: 11	2·96	97	3	,,	,,
4	67·4	0	500	,,	0: 16	2·82	95	5	,,	,,
5	67·4	0	440	,,	0: 10	2·76	97	3	,,	,,
6	79·7	0	500	,,	0: 4	2·99	98	2	,,	,,
7	76·8	0	500	,,	0: 6	3·35	98	2	,,	,,
8	78·1	0	500	,,	0: 29	3·21	95	5	,,	,,
9	78·1	0	500	,,	0: 20	3·03	95	5	,,	,,
10	80·8	0	500	,,	0: 19	3·33	99	1	,,	,,
11	81·4	0	500	,,	0: 12	3·06	95	5	,,	,,
12	74·0	0	500	,,	0: 30	3·48	95	5	,,	,,
13	80·8	0	500	,,	0: 6	3·06	97	3	,,	,,
14	80·6	0	500	,,	0: 5	3·14	97	3	,,	,,
15	79·8	0	500	,,	0: 22	3·53	98	2	,,	,,
16	80·1	0	500	,,	0: 12	3·24	98	2	,,	,,

TABLE III.—*Females with Low Androgyny Score*

No.	Androgyny Score	Blood Chromatin: Observed: No. of Nodules	Blood Chromatin: Observed: No. of Neutrophils	Blood Chromatin: Calc.: Nodules in 500 Neutrophils	Blood Chromatin Assessment	+Eosinophils	Mean Lobe Count	Buccal Mucosa Chromatin: % Neg.	Buccal Mucosa Chromatin: % Pos.	Buccal Mucosa Chromatin Assessment	Overall Nuclear Sex Assessment
1	69·9	8	120	33	+	0: 5	—	74	26	+	Pos.
2	64·1	38	500	38	+	0: 8	3·10	64	36	+	,,
3	70·7	20	500	20	+	1: 7	2·94	74	26	+	,,
4	67·4	21	400	26	+	2: 7	2·82	70	30	+	,,
5	69·9	2	189	5	+	0: 0	2·84	70	30	+	,,
6	65·4	8	320	13	+	2: 20	3·06	78	22	+	,,
7	71·0	20	500	20	+	1: 4	2·96	70	30	+	,,
8	67·2	5	300	8	+	0: 2	2·94	77	23	+	,,
9	71·4	42	500	42	+	1: 5	3·1	78	22	+	,,
10	69·3	21	500	21	+	4: 29	3·26	78	22	+	,,
11	71·7							77	23	+	,,
12	71·9	10	500	10	+	0: 5	2·5	62	38	+	,,
13	67·6	25	500	25	+	0: 10	3·32	69	31	+	,,
14	70·1	9	500	9	+	0: 8	2·78	76	24	+	,,
15	69·9	11	500	11	+	2: 46	3·23	75	25	+	,,
16	69·3	15	500	15	+	0: 3	3·2	81	19	+	,,
17	69·9	17	500	17	+	0: 4	2·92	73	27	+	,,
18	65·3	23	500	23	+	0: 5	3·26	83	17	+	,,
19	68·6	25	500	25	+	1: 12	3·32	63	37	+	,,
20	67·3							62	38	+	,,

Discussion

The possibility of an anomaly in nuclear sex associated with an abnormality of body-build in schizophrenics has been examined, but according to the methods used in this investigation there appears to be no significant relationship of this kind. Thus the striking difference in physique between schizophrenics and normal subjects remains unexplained on this basis. As the marked increase in width of the biacromial diameter occurs during the adolescent growth spurt under the influence of the sex hormones, it seems most likely that the abnormality in physique of schizophrenics is related to endocrinological abnormalities occurring at that time. This in turn may be genetically determined or produced by environmental disturbances during the period of the child's growth. The other possibility is that this narrow physique possessed by so many schizophrenics is not related to sexual development but rather to a general factor of "narrowness." This appears unlikely, as the other breadth measurement made during the examination of schizophrenics—the bi-iliac diameter—shows no significant deviation from normal (Rey and Coppen, 1959).

Summary

The primary aim of the present investigation was to examine schizophrenics for anomalies of nuclear sex. Abnormal mean androgyny scores and mean biacromial diameters had already been found in groups of schizophrenics. As these values appear closely related to sexual development, it was considered an economical screening method to select schizophrenics with highly abnormal androgyny scores for cytological examination. The deviations from normal of mean androgyny scores for both male and female schizophrenics were in accordance with previous findings.

Cytological examination failed to reveal anomalies of nuclear sex in 16 male and 20 female schizophrenics

with a maximum deviation from normal with respect to the androgyny score.

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CORTISONE AND SKIN SENSITIVITY TO TUBERCULIN IN RETICULOSES

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There have been several reports on the effect of cortisone and corticotrophin on skin sensitivity to tuberculin in a variety of diseases but not in malignant diseases of lymphoreticular tissue. Excluding tuberculosis and sarcoidosis, most workers have found that sensitivity is reduced by systemic cortisone (Carey *et al.*, 1950; Long and Favour, 1950; Lovell *et al.*, 1953), although a variable response was reported by Sulzberger *et al.* (1951). Truelove (1957) noted, however, that the Mantoux reaction became positive in 20 out of 24 patients with various diseases during treatment with prednisolone and cortisone.

In sarcoidosis Citron and Scadding (1957) reported that 57% of the patients were insensitive to 100 tuberculin units (T.U.) of purified protein derivative (P.P.D.) and that half of these became sensitive when cortisone was injected with the tuberculin. This was not just a local effect, as systemic cortisone had a similar action (Pyke and Scadding, 1952). The same occurred in patients suffering from tuberculosis who had been desensitized to P.P.D., and Citron and Scadding concluded that, since the result in sarcoidosis was identical with that in desensitized patients with tuberculosis, there was a causal relationship between tuberculosis and sarcoidosis in the patients they investigated.

Patients with malignant disease of lymphoreticular tissue form another group frequently insensitive to tuberculin (Hoyle *et al.*, 1954). The purpose of this study was to determine the effect of cortisone on tuberculin sensitivity in such patients in order to ascertain whether those who were insensitive responded in the same way as Citron and Scadding's patients with sarcoidosis.

Selection of Cases

Three groups of patients, totalling 297, have been studied: (1) 138 patients with reticuloses (aged 18–76); (2) 43 patients with carcinoma (aged 35–77); and (3) 116 controls (aged 18–78).

The term "reticulosis" is used to include all primary malignant diseases of lymphoreticular tissue. These have been classified under the headings of Hodgkin's disease, reticulum-cell sarcoma, multiple myelomatosis, lymphosarcoma (including lymphoid follicular reticulosis or Brill–Symmers disease), chronic lymphatic leukaemia, myeloproliferative syndromes (including chronic myeloid leukaemia, myelosclerosis, myelofibrosis, and polycythaemia rubra vera), and acute leukaemia (including acute erythromyelosis).

In the patients with carcinoma the primary sites included breast, bronchus, bladder, kidney, liver, pharynx, stomach, and thyroid.

The controls consisted of patients suffering from diseases unrelated to any form of malignant or reticuloendothelial disorders. These included ischaemic heart disease, cerebrovascular disease, chronic rheumatic heart disease, hypertension, a variety of infections (excluding tuberculosis), ulcerative colitis, senile osteoporosis, pernicious anaemia (treated), iron-deficiency anaemia, rheumatoid arthritis, osteoarthritis, prolapsed intervertebral disk, epilepsy, peptic ulceration, diabetes mellitus, obesity, malabsorption syndromes, cirrhosis hepatitis, and anxiety neurosis.

Technique

The technique used was very similar to that of Citron and Scadding (1957). The P.P.D. was supplied by the Ministry of Agriculture and Veterinary Research Laboratory, Weybridge (0.00002 mg. of P.P.D. is equivalent to 1 T.U.). Dilutions containing 10 T.U. and 100 T.U. in 0.05 ml. were prepared every four weeks and stored at 4° C. Just prior to injection this was mixed with 0.05 ml. of physiological saline (without preservative) to make a final dilution in 0.1 ml. The injection of tuberculin plus cortisone was prepared by mixing 0.05 ml. of the appropriate P.P.D. solution with 0.05 ml. of cortisone acetate suspension containing 1.25 mg. of cortisone acetate.

On admission each patient received an intradermal injection of 10 T.U. into one arm, and 10 T.U. plus cortisone into the other arm. Those who were negative to these were tested with 100 T.U. with and without cortisone.

TABLE I.—*Results of Testing with Tuberculin Alone*

Disease	No. of Patients	Sensitive to 10 T.U.		Sensitive to 100 T.U.		Insensitive to 100 T.U.		Significance Tests
		No.	%	No.	%	No.	%	
Reticuloses:								
Hodgkin's disease	40	2	5	16	40	22	55	
Reticulum-cell sarcoma ..	9	2	22	1	11	6	67	
Multiple myelomatosis ..	16	7	44	4	25	5	31	$\chi^2=20{\cdot}11$
Lymphosarcoma	12	5	42	2	16	5	42	d.f.=8
Chronic lymphatic leukaemia ..	15	7	47	1	6	7	47	P<0.01
Myeloproliferative syndromes	28	10	36	10	36	8	28	
Acute leukaemia	18	5	28	4	22	9	50	
Total ..	138	38	27·5	38	27·5	62	45	$\chi^2=50.9$ d.f.=2 P<0·001
Controls ..	116	82	71	20	17	14	12	
Carcinoma ..	43	18	42	17	40	8	18	

The area of induration produced by these injections was measured at 48 and 72 hours, the latter being taken as the final reading. This was done because it has been suggested that cortisone prolongs the retention of tuberculin at the site of injection, and therefore to avoid false-negative results it was decided to accept the later reading. In fact, there was no significant difference between the results at 48 and 72 hours.

The maximum and minimum diameters of the areas of induration were recorded, and any reaction having a mean diameter of 5 mm. or more was regarded as positive. In most patients a small white nodule measuring at the most 3 by 3 mm. was present where cortisone had been injected, presumably due to the slow absorption of the cortisone particles.

Many patients were also tested with injections of 0.05 ml. of cortisone acetate suspension mixed with an equal volume of physiological saline as controls. Like Citron and Scadding (1957) we found no case showing a significant response with cortisone alone.

Effect of Tuberculin Alone

The results of the reactions to tuberculin alone are shown in Table I. The patients have been divided into three groups—those sensitive to 10 T.U., those sensitive to 100 T.U.; and those insensitive to 100 T.U. 45% of the patients with reticuloses were insensitive to 100 T.U., compared with 12% of the controls and 18% of the patients with carcinoma. The difference between the reticuloses and the controls is highly significant ($P<0.001$) and is similar to that in the series of Hoyle *et al.* (1954), in which 47% of the patients with reticuloses and 44% of those with sarcoidosis failed to respond to a 1 in 100 dilution of old tuberculin which contains 100 T.U. The incidence of insensitivity to tuberculin in the patients with carcinoma resembles that of the controls, suggesting that the suppression of the reaction in the reticuloses is a special property of these diseases and not merely an expression of malignant disease in general.

There are some interesting differences in the responses to 10 and 100 T.U. In the patients with the reticuloses and in those with carcinoma, the same number responded to 10 as to 100 T.U., in marked contrast to the controls, in whom 71% responded to 10 T.U. but only 17% to 100 T.U. The same phenomenon was found by Hoyle *et al.* (1954), who used similar controls. Their patients with reticuloses and sarcoidosis responded in equal numbers to 10 and 100 T.U., while 61% of the controls responded to 10, and only 18% to 100 T.U.

In Hodgkin's disease only 2 patients (5%) responded to 10 T.U., while 16 (40%) were positive with 100 T.U. The other reticuloses show an equal distribution between 10 and 100 T.U., except for chronic lymphatic leukaemia, in which 7 (47%) responded to 10 T.U. and only 1 (6%) to 100 T.U.

Effect of Cortisone on Tuberculin Sensitivity

Patients Sensitive to 10 T.U.—38 patients with reticuloses, 18 with carcinoma, and 82 controls were sensitive to 10 T.U. The effect of cortisone on the size of the reactions is shown in Table II. There was no real change in many of the responses, but the trend was towards a reduction rather than an increase in sensitivity. There is no significant difference between the results in the three groups. Six patients (16%) with reticuloses, 3 (17%) with carcinoma, and 5 (6%) of the controls were positive with 10 T.U. alone but negative with 10 T.U. plus cortisone.

TABLE II.—*Effect of Cortisone on the Size of the Responses in Patients Who Were Sensitive to Tuberculin*

Sensitive to	Disease	No. of Patients	Change in Size of Responses in Millimetres	
			Mean Change	Standard Error
10 T.U.	Reticuloses	38	−1·9	0·7
	Controls ..	82	−1·4	0·6
	Carcinoma ..	18	−1·1	1·3
100 T.U.	Reticuloses	38	−3·5	0·9
	Controls ..	20	−3·2	1·2
	Carcinoma ..	17	−3·9	1·5

Patients Sensitive to 100 T.U.—38 patients with reticuloses, 17 with carcinoma, and 20 controls were sensitive to 100 T.U. (Table II), and there is the same trend as with those sensitive to 10 T.U., only the effect is more marked, and again there is no significant difference between the three groups: 9 patients (24%) with reticuloses, 3 (18%) with carcinoma, and 3 (15%) of the controls were positive with 100 T.U. alone but negative with 100 T.U. plus cortisone.

Patients Insensitive to 100 T.U.—62 patients with reticuloses, 8 with carcinoma, and 14 controls were insensitive to 100 T.U. In most patients with reticuloses cortisone had no effect on the reaction, but in 5 (8%) there was a positive reaction with 100 T.U. plus cortisone but not with 100 T.U. alone, though the largest response was only 6.5 mm. mean diameter. One (7%) of the controls but none of the patients with carcinoma became positive with 100 T.U. plus cortisone. One of the patients with Hodgkin's disease was initially tested twice and found to be insensitive to tuberculin alone, but responded to 100 T.U. plus cortisone on both occasions. Further testing six and eight months later showed insensitivity to both.

Discussion

The reason for the suppression of tuberculin sensitivity in patients with reticuloses is unknown, and until recently the same could have been said of sarcoidosis. However, the work of Pyke and Scadding (1952) and of Citron and Scadding (1957) suggested that there was a causal relationship between tuberculosis and sarcoidosis, for 50% of the patients with sarcoidosis, who were insensitive to tuberculin alone, responded to tuberculin plus cortisone, and the same phenomenon occurred with patients suffering from tuberculosis who had been desensitized to tuberculin. Our results in patients with reticuloses are quite different. Only 8% of insensitive patients with reticuloses and 7% of the controls became sensitive when cortisone was injected with the tuberculin.

This supports the view that the mechanism of suppression of tuberculin sensitivity in sarcoidosis is different from that in the reticuloses, but it does not help to explain the mechanism in the latter.

We considered the following possibilities to explain the suppression of tuberculin sensitivity in patients with reticuloses. First, the duration of the disease; secondly, the severity of the disease; thirdly, steroid therapy; fourthly, that it was simply an expression of grave illness due to a malignant disease; fifthly, that there

was some abnormality of the lymphocytes; and, finally, that it was one expression of a general failure in the normal immunity mechanism.

The duration of the disease, as judged by the interval between diagnosis and testing with tuberculin, has no effect on the incidence of tuberculin sensitivity. Only 13 (46%) out of 28 patients who had been diagnosed for less than one month responded to tuberculin compared with 32 (48%) out of 66 who had been diagnosed for six months or more.

There was a possible correlation, however, between the severity of the disease as judged by the interval between testing and death, and the incidence of tuberculin sensitivity. Of 22 patients tested for the first time in the month prior to death, 8 (38%) were sensitive. Of 29 patients who died more than three months after testing, 17 (59%) were sensitive. The difference is not statistically significant but does suggest that there may be a reduction in tuberculin sensitivity just before death. In each of these two groups five patients were receiving steroid therapy, so that this probably does not account for the difference, and there was no correlation with any particular variety of reticulosis.

Of 16 patients receiving prednisolone or triamcinolone at the time they were first tested, nine (56%) were insensitive. This result does not differ significantly from the patients who were not receiving steroid therapy, but it suggests that, in contrast to sarcoidosis, systemic steroids depress rather than enhance tuberculin sensitivity. This is supported by the few sensitive patients who have been tested repeatedly. Six patients sensitive to 10 T.U. and four responding to 100 T.U. were studied. Of those sensitive to 10 T.U., three remained unchanged over a period of 18 months and three showed a reduction in tuberculin sensitivity. Of those that remained unchanged, two never received steroids and the third was on prednisolone throughout the period. Of the three who showed reduced sensitivity two failed to respond to both 10 and 100 T.U., while the third reacted only to 100 T.U. These three patients had never received steroids prior to the first test but were all receiving prednisolone at the time of the final test.

The same occurred with the four patients sensitive to 100 T.U.; two of them remained unchanged, one receiving steroid therapy the whole time, and the other was never given steroids. The two who became insensitive over a period of one year had not received steroid therapy on the first occasion, but were being treated with prednisolone at the time of the final test. None of the patients who were originally insensitive developed sensitivity during the course of the disease.

From this it would appear that systemic steroid therapy can undoubtedly suppress tuberculin sensitivity in patients with reticuloses, but all these patients had deteriorated during the period of testing, so that increased severity of the disease may have played a part in suppressing sensitivity.

This suggests that although there is no correlation between the duration of disease and the incidence of tuberculin sensitivity in the reticuloses, both steroid therapy and increasing severity of disease may suppress tuberculin sensitivity. However, neither of these two factors alone or in conjunction is sufficient to explain the marked suppression of tuberculin sensitivity in these patients, though they may both contribute to it.

Suppression of the Mantoux reaction is not a feature of other forms of malignant disease—that is, carcinoma—for these behave more like controls than patients with reticuloses.

There is much evidence to suggest that delayed allergy of all types, including the tuberculin reaction, depends on lymphocytes, for such sensitivity can be transferred from one subject to another only by lymphocytes (Wesslén, 1952; Chase, 1955; Braunsteiner *et al.*, 1958). It might be expected, therefore, that the diseases specifically involving lymphocytes (chronic lymphatic leukaemia and lymphosarcoma) would show a higher incidence of tuberculin insensitivity than the other reticuloses. However, this is not so, for of 27 patients with these diseases only 12 (44%) failed to respond to 100 T.U., which is similar to many of the other reticuloses. In fact, it is less than in Hodgkin's disease, in which 55% of the patients were insensitive. Testing with 10 T.U. showed that 95% of the patients with Hodgkin's disease failed to respond, compared with 52% with chronic lymphatic leukaemia and lymphosarcoma.

Patients with sarcoidosis and reticuloses have been shown to be poor producers of antibody on primary immunization with tetanus toxoid (Greenwood *et al.*, 1958), and it has been suggested that the suppression of tuberculin sensitivity is a manifestation of failure of the normal immunity mechanisms. However, the mechanism for producing humoral antibodies is quite different from that involved in delayed hypersensitivity, for patients with agammaglobulinaemia who cannot form circulating antibodies can be made sensitive to tuberculin by vaccination with B.C.G. (Porter, 1955). Further, the serum gammaglobulin level and the titres of iso-agglutinins to the ABO blood groups are often very low in chronic lymphatic leukaemia and multiple myelomatosis, in contrast to the other reticuloses (Fairley, 1959). However, the incidence of insensitivity in these diseases of the lymphocyte–plasma-cell series is lower than that of Hodgkin's disease and reticulum-cell sarcoma. Thus the failure to produce humoral antibodies is not closely correlated with decreased sensitivity to tuberculin.

Therefore we can only conclude that the mechanism of suppression of tuberculin sensitivity in patients with reticuloses is still obscure, but it is clearly different from sarcoidosis.

Summary and Conclusions

Skin sensitivity to tuberculin with and without local cortisone has been determined in 138 patients with reticuloses, 43 patients with carcinoma, and 116 controls.

The previous reports that tuberculin sensitivity is depressed in reticuloses have been confirmed, 45% of the patients with these diseases being insensitive, compared with 18% of those with carcinoma and 12% of the controls. Possible reasons for this are discussed.

In the patients who responded to 10 or 100 T.U., cortisone tended to reduce the size of the reactions in all three groups, an effect which was more marked with 100 than with 10 T.U.

In the patients who were insensitive to tuberculin, 8% of those with reticuloses, 7% of the controls, but none of those with carcinoma gave a positive reaction with tuberculin plus cortisone. This is in contrast to

the findings of Citron and Scadding (1957) in sarcoidosis, where 50% of the patients who were insensitive to tuberculin alone gave a positive reaction with tuberculin plus cortisone. This suggests that the mechanism of suppression of the tuberculin reaction in sarcoidosis is different from that in the reticuloses. The implications of these results are discussed.

In a patient who is insensitive to tuberculin the development of sensitivity when cortisone is added suggests, but is not diagnostic of, sarcoidosis rather than one of the reticuloses.

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A TRIAL OF DISCHARGE AND AFTERCARE OF LONG-STAY MENTAL HOSPITAL PATIENTS

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Even if it should be possible in the future to avoid entirely the accumulation of chronic patients in mental hospitals, there remains the immediate task of discharging into the community, and if possible into regular employment, those patients who do not present any marked behaviour problems due to their illness, but are still in hospital for social or other reasons.

The Investigation

This paper reports on a review of 223 long-stay male patients from one hospital made to assess those who could be discharged immediately and to overcome, with the help of a psychiatric social worker, the difficulties in the way of their discharge. The hospital is one of those in which investigations by Garratt *et al.* (1957, 1958) have shown that about 12% of such patients exist, and similar findings have been made by Cross *et al.* (1957) in the same hospital. Not included in our review were patients in the sick ward, in the "refractory ward," or from the two annexes of the hospital in other parts of the city. Female patients were excluded for administrative reasons only, though it is clear that the chronic female population is of greater practical importance. The review itself took from January, 1957, to September, 1958, but this paper covers the period from January, 1957, to January, 1950, in order to include the follow-up results.

The hospital is old and overcrowded and stands in a densely populated industrial area. Modernization schemes have improved the accommodation and facilities for the patients. The catchment area includes the city centre with its doss-houses, prison, lock-up, reception centre, and busy casualty departments. The patients in the five long-stay male wards which we have investigated have all been treated by drugs, and other physical methods over recent years. Lately, individual and group treatment along social and occupational lines has been increasingly applied.

In 1955 about 40% of the male patients were not working and 38% were occupied with ward work only (Cross *et al.*, 1957). At the time of our review 20% of the patients were unemployed in the hospital, and 18% were occupied with ward work only.

Because of severe overcrowding, arrangements were made, towards the end of 1956, for a psychiatric social worker of the City of Birmingham Public Health Department to assist the hospital staff in the discharge and aftercare of patients. The intention was to make a detailed investigation of long-stay patients, to select those considered fit for discharge, and to provide aftercare for them. Tables I and II set out data about the 38 patients discharged.

Each patient was interviewed and assessed individually. The doctor usually began the interview and led up to the special point at issue in the case. The interview was then continued by the social worker. We were careful to tell the patient why he was being seen and to seek his views about our suggestions. All decisions were taken with the patient's knowledge and consent. This procedure proved time-consuming, and as a rule we interviewed six to eight patients in a two-hour session.

We found that 45 patients (20%) were neither having leave nor being visited. After 15 relatives had been approached by the social worker five families began visiting.

Where relatives were already visiting regularly, the question of day or week-end leaves was discussed. Seventeen relatives were approached, and this led to regular leaves for 10 patients.

In other cases, where regular leaves had led to no difficulties, relatives were encouraged to have the patients to live at home. Seven patients were discharged and attended the hospital daily for periods of from three days to three years. Their families appreciated this arrangement, because the patients were supervised and occupied during the day and, if necessary, kept under treatment. The scheme also helped patients who, though they seemed fit, could not immediately find suitable employment.

In this area, and probably in other industrial cities, employability is an important factor when considering

a patient's discharge (Cross *et al.*, 1957). The families have often changed greatly during the absence of long-stay patients and there is little willingness to accept one who is now a stranger and unable to support himself. In doubtful cases, we were fortunate to have the advice of a clinical psychologist, especially experienced in vocational guidance, in deciding whether the patient was suitable for referral to an industrial rehabilitation unit. He saw 27 patients, of whom 17 later attended the local I.R.U. while still living in the hospital. This proved a useful stage in overcoming institutionalization and in the assessment and development of patients' ability to work. We arranged for two other patients to travel daily to work from the hospital.

When discharge seemed probable the social worker helped the patient to plan for the future. Sometimes the offer of practical help was all that was needed, but, when encouraged to talk about their feelings, most patients expressed considerable anxiety and clearly felt somewhat inadequate to face the outside world. They needed much reassurance and asked for the continued support of doctor and social worker. Nevertheless, as much responsibility as possible was placed on the patients to make their own decisions and arrangements. In the ensuing months several patients came, of their own initiative, to the social worker with personal problems, and the therapeutic value of the relationship established while the patient was still in hospital was obvious.

When visited by the social worker most relatives showed some ambivalence towards the patient, and those who agreed to have him home welcomed the offer to keep in touch and be available in case of difficulties. Reassurance and advice were as much sought by relatives and landladies as by the patients.

We encouraged those patients who had no home available, but could work, to move into lodgings. Great efforts were made to find landladies who would accept former mental hospital patients, but with little success. Fortunately, one lodging-house keeper took, in all, 11 patients for varying periods. Altogether 16 patients were found lodgings; two found their own accommodation in Salvation Army hostels.

Despite their dependent attitude before and during the first two or three weeks after discharge, we noted the independence and initiative shown by some patients once they had settled in their new surroundings—for example, the social worker was able to find a job for only one patient, but the others found work by themselves or through the Labour Exchange.

Most patients who left hospital continued to receive medication, and some of them were followed up at the out-patient clinic for a few months. The social worker also kept in touch with the majority.

TABLE I.—*Discharged Patients who Remained Out of Hospital on January* 31, 1960

Case	Age on Discharge (Av. 43)	Length of Stay in Years (Av. 11½)	I.R.U.	Period of Discharge under Review in Months	Work Record (Months)	Living Accommodation
1	51	24	Yes	31	26	Home
2	29	10		26	Nil	,,
3	44	24	,,	32	32	Lodgings
4	52	18		33	14	,,
5	24	1	,,	34	34	,,
6	53	1		30	Not known	Home
7	37	21		32	Nil	,,
8	50	13		31	20	Lodgings
9	45	8	,,	24	24	Home
10	59	29		27	24	,,
11	45	6		36	Nil (day patient)	,,
12	29	5		24	Not known	Home to Ireland
13	31	8		21	,, ,,	Home to B.W.I.
14	50	9		21	21	Home
15	45	10		16	Nil	Lodgings
16	49	17		24	,,	,,
17	50	3 times in a year		16	13	,,
18	37	6		19	16	Home
19	47	20		21	3	Lodgings
20	54	3	Yes	15	Nil (day patient)	Home
21	43	22	,,	4	4	,,
22	38	10	,,	6	6	,,
23	52	21	,,	12*	4	Lodgings
24	40	6	,,	35*	31	Lodgings and home
25	23	6 times in 4 years	,,	18†	Not known	Home
26	42	17 and previously	,,	28‡	2	Lodgings
27	47	2 and twice previously	,,	32§	14	,,
28	39	4		6. Died	2	,,

* Includes further admission of three months. † Includes further admission of six months. ‡ Includes two further admissions of three and four months. § Includes further admission of two months.

TABLE II.—*Discharged Patients who were Later Readmitted and Remained in Hospital on January* 31, 1960

Case	Age on Discharge (Av. 38)	Length of Hospital Stay (Av. 3 yrs)	I.R.U.	Period of Discharge	Work Record	Living Accom.	Reason for Readmission
29	32	6 mths	Yes	5 mths	Nil	Home	Schizophrenic episode
30	42	1 year		3 days	Day patient	,,	Anxiety symptoms
31	56	3 years		10 ,,	Nil	,,	Schizophrenic episode
32	28	3 ,,		1 mth	,,	Lodgings	Death of father, depression
33	38	5 times in 4 years	,,	4 mths	,,	,,	Schizophrenic episode
34	47	6 mths		2 wks	,,	,,	Confusional state
35	24	1 year		6 mths	6 mths	,,	Court order after petty larceny
36	32	6 times in 8 years	,,	10 ,,	Day patient	Home	Family complained of behaviour
37	45	11 yrs	,,	4 ,,	,,	,,	Attempted suicide
38	32	10 ,,	,,	1 mth	Nil	Lodgings	Schizophrenic breakdown

Three Case Summaries

Case A.—This patient, an unmarried labourer, had developed a florid paranoid schizophrenia at the age of 20, and was admitted to hospital in 1933. He remained in hospital continuously until 1957. Under treatment with chlorpromazine his psychosis became controlled and after a period at the I.R.U. he was discharged and went to live with his aged and ailing mother. He had early difficulties in adjustment and was unable to find work. However, after five months he found employment, and at the end of our survey had been working 27 months. During that time he showed increasing interest, redecorated the house, bought new floor coverings, and in general greatly improved his own and his mother's living conditions. Her health deteriorated and she needed the help of the home nursing services. Her son's presence helped to avoid her admission to hospital. Drug treatment and rehabilitation led to a partial recovery, and resettlement at home has continued the process.

Case B.—This patient, a cycle-frame builder, developed a catatonic schizophrenia at the age of 19, in 1947. Treatment included a full course of E.C.T. in 1947, with little improvement, and in 1957 a course of intensive reserpine therapy.

peak dosage 13 mg. daily. Though his behaviour became quieter and more co-operative, he remained solitary and mute. His mother was most anxious to have him home. After four week-end leaves he left the hospital and has been at home for 26 months. He is still generally mute, though he does speak occasionally. His mother is delighted with the arrangement, as she has difficulty in walking and he runs errands for her. Drug treatment led to moderate amelioration of symptoms only, and the problem appeared to be one of custodial care. His mother values his company and his help, and provides the care needed in a much more normal environment.

Discussions are being held with the Ministry of Labour about the possibility of his attending a course of industrial rehabilitation.

Case C.—This patient was a single man, a labourer, who developed florid paranoid schizophrenia in 1933 at the age of 27. He stayed in hospital continuously until 1957. Treatment with chlorpromazine led to considerable all-round improvement, and he was able to attend the I.R.U. from the hospital. He was helped to find lodgings and within a week of discharge was working. He has remained at this job since that time, and after 22 months changed his lodgings of his own initiative. This man shows the apparent ease with which some long-stay patients can settle in the community when drugs have improved psychotic symptoms. Since his discharge he has not required help from any social agency.

Discussion

The widespread use of drugs has led to a great improvement in the behaviour of long-stay patients, and this in turn has made possible an open-door policy with a growing programme of rehabilitation. The effects of these methods have shown not only in an overall improvement in the life of patients but also in the larger number of them able to be discharged. The increase in discharges is definite, though the numbers remain small, and appeared to be lessening again when this work was started. Table III gives the number of long-stay patients discharged in the years 1953–8.

TABLE III.—*Yearly Number of Long-stay Male Patients Discharged*

Year	1953	1954	1955	1956	1957	1958
No.	8	8	17	17	17	19

The increase in discharges from 1955 onwards can be attributed to the long-term benefit of drug treatment and the consequent renewed interest in the long-stay wards.

Thus, despite these improvements, together with the work described, no great number of discharges has resulted, nor at present could this be conscientiously predicted. We have tried to assess why only 28 patients (12%) could be discharged to remain out of hospital, and have grouped those patients who were still in hospital at the end of our inquiry under three headings, as follows:

Group 1.—Patients whose mental condition made resettlement in the community impossible: 165 (85%).

Group 2.—Patients capable of living outside hospital but considered unfit for work and without relatives willing to have them because of residual symptoms or lack of accommodation: 14 (7%).

Group 3.—Patients who might easily become employable and could benefit from living under supervision in sheltered hostel accommodation. These patients could not cope with life in the type of lodgings obtainable: 16 (8%).

These groupings are approximate, but to us it seems true that the vast majority of patients were unable to leave hospital because of their mental state rather than for social reasons. In their study of four Birmingham mental hospitals, Garratt *et al.* (1957, 1958) found that 13% of the male patients did not require hospital facilities—a finding which is comparable with our groups 2 and 3. They also estimated that 119 (8.8%) required only the support of an organized community (cf. group 3).

What is here described as a specially arranged investigation should be part of the routine work of psychiatrist and social worker. By joint initiative, regular meetings now take place between hospital staff and social workers of the local authority. It is only an apparent paradox that aftercare should begin before patients leave hospital. A social worker should see the patient before discharge, so as to offer practical help and encouragement. If the patient leaves hospital knowing the kind of difficulties that lie ahead, yet also knowing that at least one person in his new community understands his needs, he is likely to have more confidence and his chances of making a satisfactory adjustment will be increased.

Of the 15 readmissions during the three-year period, 10 occurred within one year of discharge. Brown *et al.* (1958) found that of the relapses during six years after discharge, 74% in schizophrenics and 58% in non-schizophrenics occurred within the first year. The higher relapse rate during the first few months after discharge confirms the need for adequate psychiatric aftercare, and also points to a need for hostel accommodation, which would make possible a gradual reintroduction of patients into the community and closer supervision than is otherwise possible.

Summary

During an inquiry into the individual needs of 223 male patients in the chronic wards of a mental hospital in an industrial city it was found possible to discharge 38 patients. Fifteen were readmitted within the period of the survey (though five were again discharged). The work was jointly undertaken by a hospital psychiatrist and a psychiatric social worker from the local health authority.

The inquiry illustrates the necessity for the social worker who is to provide aftercare to make an initial contact with the patient before he leaves hospital; it also suggests a need for hostels to help patients in the transition from a long stay in hospital to a normal life outside.

We thank Dr. J. J. O'Reilly, medical superintendent of All Saints' Hospital, for permission to carry out this survey, and Dr. W. Mayer-Gross for his advice and help in preparing this paper.

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Medical Memoranda

Temporal (Giant-cell) Arteritis Associated with Gangrene of Scalp

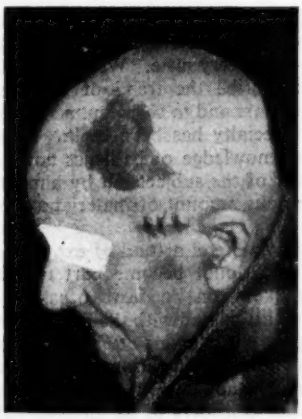
The entity of temporal arteritis has become firmly established in recent years and has been the subject of many exhaustive surveys. Its many complications are well known, but we have found only two recorded cases in which gangrene of the scalp was associated with this disorder. A further case is presented.

CASE REPORT

An 85-year-old man was admitted to hospital in September, 1958, with a 10-months history of diffuse headache. Early in the course of his disease his daughter noticed striking inflammation of the temporal arteries; this subsided after some six months. Just before his admission he had fallen and become confused. He was admitted for observation. During his three-weeks stay in hospital his confusion lessened. A constant finding was an evening pyrexia of 99° F. (37.2° C.). Investigations showed a persistent neutrophil leucocytosis (13,000–20,000/c.mm.) and a constantly elevated E.S.R. of 48 mm./hour (Wintrobe). He was discharged without a firm diagnosis being made.

Ten days after his discharge he developed symmetrical dry gangrenous areas over both temporal regions. At the same time he became aware of blindness in the right eye.

He was readmitted to hospital 10 days after the appearance of the gangrene. Examination showed him to have bilateral symmetrical areas of dry gangrene over both temporal regions, each lesion being approximately 5 by 2½ in. (12.5 by 6.4 cm.). The temporal arteries were palpable as firm cords without pulsation. The occipital arteries were palpable and tender, but there was some discernible pulsation. The whole scalp was tender. Ophthalmoscopic examination showed a normal left eye. In the right eye there was a marked diminution and irregularity in the calibre of the retinal arteries. Some appeared empty in places. The disks were normal, but vision was less than 6/60.



The patient felt intensely miserable and when left alone sat holding his hands to his head. The E.S.R. was still 49 mm./hour (Wintrobe) and there was a persistent leucocytosis of 11,700/c.mm., with 66% polymorphs.

A biopsy of the left temporal artery was performed under local anaesthesia. The report on the histology by Dr. J. O. Mercer confirmed the diagnosis of temporal arteritis. "In the wall of the vessel were granulomatous lesions with giant cells. These extended from the intima into the media, and the internal elastic lamina was fragmented."

The patient's response to prednisone, 40 mg. daily, was remarkable. Within 48 hours the headache of some 12 months' duration had gone.

The gangrenous areas were kept dry and protected. Over the next few months healing occurred slowly from the edges. A low-grade infection at the edge of the slough was easily controlled by eusol dressings.

Re-epithelization was complete without skin-grafting. The new skin which covers the former necrotic area is now firmly adherent to the periosteum. The disk of the right eye shows optic atrophy. The E.S.R. remains elevated at 20–30 mm. (Wintrobe).

The dosage of daily prednisone and of weekly corticotrophin gel have been reduced, guided by clinical response (freedom from headache) and more particularly the E.S.R. At present, 14 months later, he still needs 5 mg. of prednisone daily and is also given "acthar gel," 10 units weekly. Physically and temperamentally this man is now his former cheerful self.

COMMENT

While temporal arteritis is an uncommon disease, gangrene of the scalp is a striking if rare complication. Roux (1954), in his review of 248 cases, found it recorded only once; this case, recorded by Riis (1947), was similar to ours. We have been able to trace a further case reported by Tirschek (1957).

The scalp is known to have a very rich anastomotic arterial blood supply, receiving the supraorbital and supratrocheal arteries from the internal carotid artery via the ophthalmic artery, and the superficial temporal, the posterior auricular, and the occipital arteries from the external carotid artery. To produce gangrene the disease process must involve most if not all these branches. In the above case there is evidence of involvement of the ophthalmic as well as the temporal arteries, and this frequent association has led to the use of the term "cranial arteritis."

Our case shows the occurrence of the serious complication of blindness which occurs in a large proportion of cases. Harrison (1948) found it in 25 out of 75 cases recorded up to that time, while Birkhead *et al.* (1957) found evidence of bilateral blindness in 22% of 250 untreated cases. The latter also showed conclusively the great value of adrenal steroid therapy in this as yet obscure disease. In 55 treated cases there was no further deterioration in vision.

We thank Dr. H. Barnett for referring this case, and Mr. Wynn-Jones, of Roche Products Ltd., who kindly supplied some of the references.

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Everybody's Business: The 1959 Mental Health Act and the Community, by Nesta Roberts, deals with the opportunities now given to local authorities, voluntary bodies, and the man in the street to play a part in bringing about new understanding for those who are mentally ill. The booklet is available from the publishers, the National Association for Mental Health, 39, Queen Anne Street, London, W.1, at 1s. 6d. (1s. 10d. by post).

Reviews

CARCINOGENESIS BY CHEMICAL COMPOUNDS

Bibliography of Cancer Produced by Pure Chemical Compounds. A Survey of the Literature up to and Including 1947. By Otto Neubauer, M.D. (Pp. 604+xxvii. 42s.) London: Clarendon Press, Oxford University Press. 1959.

For those of us who are too busy with other problems or "too lazy" to search for the literature ourselves, a book like the one under review is invaluable. It is true that it treats of only one subject, carcinogenesis by chemical compounds; but this topic is of such importance in fields outside cancer research—general medicine, public health, nutrition, food and dye-stuff manufacture, and so on—that the late Sir Ernest Kennaway's suggestion inspiring the book was an excellent one.

The usual technique in creating a bird's-eye view of a chapter of scientific medical research is to write a survey. The person charged with this task will, as a preliminary, collect pertinent references and then spin his yarn around the accumulated bibliography. This method was not adopted in the present case. What has been done instead was to assemble all references to published work on the subject up to and including 1947 under the headings of author index and subject index. The latter was then subdivided into main sections such as chemical properties, biological data, diet and vitamins, mode of action, and many more, and each main section was broken up into subsections—polycyclic compounds, sterols, etc. All this allows for a very rapid search for specific papers or a quick survey of the contributions to a certain aspect of the field. Maybe some of us would have preferred an issue of loose index cards (as is being done with data on spectroscopy), but this would have required boxes or a drawing cabinet. The bound volume, printed in a clear type, can be placed on our bookshelves or on the writing desk, and the thousands of references remain together awaiting the moment for being looked at by anybody interested in the still mysterious process of carcinogenesis by exogenous means.

F. BERGEL.

LEGALIZED ABORTION

Somatic Complications Following Legal Abortion. By Jan Lindahl. Translated by S. H. Vernon. (Pp. 182. 42s.) London, Melbourne, Toronto: William Heinemann Medical Books Ltd. 1959.

The publication of this book is particularly welcome at a time when arguments rage for and against therapeutic abortion, and when certain countries are considering legalizing abortion for eugenic and social indications. In the foreword, Dr. Westman says that, following the legalization of abortion by the Swedish Government in 1938, the incidence of the operation came to represent 5% of deliveries. Interestingly enough, however, and despite no change in the law, the incidence has fallen in the last few years. The reasons for this are not discussed here, and there is nothing to suggest that it is the result of psychological and somatic ill-effects of induced abortion. A review of psychological reactions among patients in Sweden was published by M. Ekblad in 1955. Dr. Lindahl now describes the effects on the physical health of 1,188 women whose pregnancies were terminated in six gynaecological units in Stockholm during 13 months, 1952 to 1953. One thousand one hundred and thirty-three of the patients were examined three weeks after operation, and 1,013 were examined again one to five years later. This represents a remarkable "follow-up" success rate.

In all except 84 cases, the indication for the operation was "mental disease," "weakness," "foreseen weakness," "eugenic," and "humanitarian." One woman died as a direct result of the operation, and 3.6% women suffered significant operative and post-operative complications. Nevertheless, the findings in general reveal a low incidence of persistent ill-health and sterility following abortion. One remarkable observation was the discovery of 166 cases of endometriosis of the cervix (and sometimes of the vagina and bladder as well) among 840 traced cases treated by vaginal hysterotomy—an incidence of 19.8%. The reasons for this complication and the methods whereby it can be avoided are described by Dr. Lindahl. He also devotes a chapter to a review of the world literature on the hazards of induced abortion. In all, this book represents a valuable study, admirable for its detailed, factual, and detached appraisal of one aspect of a highly controversial subject.

T. N. A. JEFFCOATE.

AN EXPERT IN MURDER

Mostly Murder. By Sir Sydney Smith, C.B.E., LL.D., M.D.(Edin.), F.R.C.P.(Edin.). Foreword by the Hon. Lord Cameron, D.S.C., D.L., LL.D., F.R.S.(E.). (Pp. 318; illustrated. 21s.) London, Toronto, Wellington, Sydney: George G. Harrap and Co., Ltd. 1959.

The title is unworthy of the book, though no doubt it will justify itself by its suggestion of sensationalism. The book does, however, offer entertainment—with a subtle blend of wisdom—for every taste. What is more, it is the first book to describe the trend of forensic science during the last 30 years and to show upon what a slender initial basis the specialty has been built. Thus Smith aquired his expert knowledge of ballistics not by working with some master of the subject but by himself toiling through the enormous amount of material at his disposal in Egypt.

The author is able to draw upon a fund of extremely good stories which will no doubt become part of the repertory of many speakers on medical occasions, excepting, of course, those associated with the Edinburgh School of Medicine. So, too, by drawing attention to the part played by Bell in inspiring the creation of Sherlock Holmes, it has been possible not only to impress upon the reader what the author considers to be the essential characteristics of the medico-legalist—or should it be the medical detective?—but at the same time to get in some gentle digs at other practitioners. It is only when the author gets on to the subject of Spilsbury that perhaps his direct sense of humanity forsakes him, for, rightly or wrongly, there is no finesse in his condemnation of what he considers to be Spilsbury's inability to change his mind.

The description of the cases in Egypt are perhaps the most fascinating reading in the book, though the author's contribution to some of those nearer home gives the reader an additional insight into them.

If any criticism is to be levied at this work, it is that it is a little too long and appears to drag at the end. Possibly the material in this part is not up to the standard of the rest, and the author is more decisive with less reason. This minor criticism—and probably many will not agree with me—does not detract from the

value of the book as a whole. It is excellent entertainment and should be read by all prospective medico-legalists and those who are. There are several excellent illustrations, perhaps the best of which is that of the author himself with Spilsbury's as a close runner-up.

F. E. CAMPS.

FOR DIABETIC GOURMETS

The Complete Cookery Book for Diabetics. By Iris Holland Rogers. Second edition. (Pp. 134+vi; illustrated. 6s.) London: H. K. Lewis and Co., Ltd. 1959.

The appearance of a second edition of this book is the outcome of a demand which can only be attributed to its popularity among intelligent diabetics themselves and those who care for them. The author combines a knowledge of the dietetic aspect of the treatment of diabetes with a personal taste for good food and a very sound practical knowledge of the art of producing it. It is not an elementary introduction to dietetics but a cookery book, and as such provides the reader with a wide range of recipes of known carbohydrate, protein, and fat values. Carbohydrate contents are expressed in terms of 10-g. portions (Lawrence black lines), and food tables arranged alphabetically add to the usefulness of the book.

Any diabetic equipped with this book and average intelligence should experience no difficulty in making a modern diabetic diet both varied and attractive. To any parent of a diabetic child this small addition to the more standardized dietary instructions provided by most diabetic clinics can only be regarded as more than handsome return for its small cost, and one which should go far to bridge the gap between the normal and the diabetic diet. With its help there should be little reason for the diabetic child to become either a thief or a liar !

The author is the Welfare Secretary of the British Diabetic Association, and her cookery book must be regarded as one of the many valuable services rendered to the diabetic community by that association. This book has not been written for doctors, but they would be well advised to bring it to the notice not only of their diabetic patients but also of all those responsible for converting diabetic diets into palatable meals.

WILFRID OAKLEY.

HISTORY OF PARASITOLOGY

Parasites and Parasitic Infections in Early Medicine and Science. By R. Hoeppli, M.D., D.Sc. (Pp. 526+xiv; illustrated. 63s.) London: Oxford University Press, for Malaya University Press. 1959.

> "Knowledge is proud that he has learn'd so much;
> Wisdom is humble that he knows no more."
> William Cowper. (*The Task.*)

These lines are aptly used by Professor Hoeppli as a heading to one part of this immense work. Its title is a little misleading, for it is not confined to history—except in the sense that history ends now. It includes many of the author's own observations in the Far East, often obtained under conditions of great difficulty. Nor does it lack the scholar's humility, some examples of which may raise a smile. Thus Plate XXII is a well-produced photo of "Sea-Dayak girls delousing each other." The writer adds a postscript saying that he "will possibly be criticized by some Sea-Dayaks who may see this plate." We think his fears ungrounded. Despite the rise of nationalist movements everywhere, I believe it will be long before this extremely learned work enters the curriculum of the girls' schools of that interestingly primitive people of Sarawak.

Dr. Hoeppli's book is hard to describe because it covers such a prodigious amount of ground. He has had access to a wide range of Chinese, Japanese, and Korean literature, where the reviewer is unfortunately unable to follow him, but he has also embraced the whole sweep of Western literature which bears—often remotely enough—on parasitology from the Greeks onwards. He also considers the mechanism by which the knowledge of the West has passed to the East and *vice versa*. The variety of information in the book is truly remarkable, though its strong point is not in its organization. It will bring news to some that an elephant figures on the black obelisk of Shalmaneser III (859–824 B.C.), and a two-horned African rhinoceros on a coin of the Roman emperor Domitian (A.D. 81–96); that two Roman emperors are alleged to have died of phthiriasis; and that recent observations leave no doubt that the breeding habits of a considerable number of marine organisms have been shown to be affected by the phases of the moon, apart from the influence of these phases on the tides.

Dr. Hoeppli includes in his inquiries helminthology, protozoology, and entomology. He has much to say on early views on the parasites shared by people of Borneo, Malaya, and China, and discusses the influence of parasites on the course of history. The origin of the names for various parasites has itself a history. It must be news to most that the word fluke is from Anglo-Saxon *floc*, a flounder, and that the creature was believed to be a sort of fish. The French form of the word *fasciole* may have been derived from, or confused with, the vernacular term for a plant, the leaves of which sheep were believed to have swallowed. For Linnaeus the *Fasciola hepatica* was a kind of leech, the young of which lived in water. There are many such adventures, even for the most learned, in this remarkable volume.

The book of its very nature will be read through by few, but it is a useful reference work for most aspects of its very wide subject, and is fortunately provided with reliable indexes. It is a good omen that so learned a work should come from one of the newer universities of the Commonwealth. The erudition of its author is truly remarkable, especially in view of his long separation from the great European libraries. The printing, which has been done in Hong Kong, is excellent.

CHARLES SINGER.*

LABOUR WITHOUT PAIN

Childbirth Without Pain. By Dr. Pierre Vellay and others. (Pp. 216; illustrated. 35s.) London: Hutchinson with George Allen and Unwin. 1959.

Analgésie Psychologique en Obstétrique. Journée d'Études sur l'Analgésie Psychologique en Obstétrique, Paris, April 7, 1957. Edited by P. Aboulker, L. Chertok, and M. Sapir. Introduction by H. de Watteville. (Pp. 172+xii; illustrated. Fr. 3,500.) Paris, London: Pergamon Press. 1959.

Dr. Vellay is the inheritor of Dr. Lamaze's mantle and has become the chief exponent of the psychoprophylactic method of preparing women for labour. The present book, which is well translated, gives a clear and full description of the method, its theory and practice. It is a little weighted with case histories, though fortunately less so than is the original. "Read's theory" is given a chapter, and students of this theory will be surprised to learn that it "does not sufficiently take into account the . . . bond between mind and body."

*This review was received shortly before Professor Singer's death on June 10.

Though partisan, the book describes a system that has, after all, brought hope and happiness to a great many mothers.

Analgésie Psychologique en Obstétrique is based much more broadly. Professor de Watteville writes the introduction and surveys the present scene. His observations strike a familiar note, for remarkably similar ones have been made by other workers, from all parts of the globe, who are seriously experimenting with psychological approaches to the relief of pain in childbirth. The paper of Mayer and Morelli-Daninos foreshadows their extremely interesting project to follow, with the help of a team which includes paediatricians and psychiatrists, the results of their method on the subsequent relations of the mother with her family. The method of preparation and management they have devised uses what they feel to be "the best of both worlds." There is perhaps a preponderance of contributions from practitioners of the "psychoprophylactic" method of preparation, but then the conference, of which this book is a record, was held on the Continent. As a whole, it offers a considerable contribution to the study of the psychological causes of pain in childbirth and of the means of dealing with them. As light relief there is a Freudian interpretation by This of the myth of Alcmena which, though entertaining, naturally contains some shrewd digs.

This is a stimulating book. It reflects the considerable attention that is being paid to the subject by our colleagues on the Continent, who are apparently more concerned about it than we are.

SHILA RANSOM.

"IATROGENIC POT-POURRI"

Diseases of Medical Progress. A Survey of Diseases and Syndromes Unintentionally Induced as the Result of Properly Indicated, Widely-accepted Therapeutic Procedures. By Robert H. Moser, B.S., M.D. Foreword by F. Dennette Adams, M.D. (Pp. 131+xvi. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The purpose of this book is to deal with "diseases that would not have occurred if sound therapeutic procedure had not been employed." It is almost entirely concerned with the ill effects or complications of the use of drugs. It omits those conditions which occur because the patient survives illnesses that were formerly fatal, such as the Kimmelstiel–Wilson kidney of the treated diabetic and the increased incidence of carcinoma of the stomach in treated pernicious anaemia. It includes some of the complications of operations. Some of the side-effects of drugs are familiar enough, such as staphylococcal diarrhoea or fungus infections after antibiotics, and agranulocytosis after antithyroid agents. Others are still fortunately a little unfamiliar, such as Parkinsonism and allied syndromes after tranquillizers.

The book is a *précis* or catalogue, and, indeed, only 58 pages are text, the remaining 73 pages being bibliography and index. However, Dr. Moser's literary style hardly encourages us to ask for more, because he can write sentences like, "The evolution of a formidable stockpile of potent therapeutic agents, improved surgical procedures, and more efficient equipment has kept this iatrogenic pot-pourri boiling." It is in fact as a compilation that this book should be reviewed, and Dr. Moser has done his task well. He has quarried out a great deal of useful material which will no doubt be built into a number of admonitory presidential addresses

L. J. WITTS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Freezing and Drying of Biological Materials. By 13 contributors. Consulting Editor: Harold T. Meryman. *Annals of the New York Academy of Sciences*, Volume 85, Art. 2. Editor in Chief: Otto V. St. Whitelock; Managing Editor: Franklin N. Furness; Associate Editor: Peter A. Sturgeon. (Pp. 501–734; illustrated.) New York: New York Academy of Sciences. 1960.

Our Adult World and its Roots in Infancy. By Melanie Klein. (Pp. 15. 3s. 6d.) London: Tavistock Publications. 1960.

Atti del Convegno di Studio su: "Esperienze di Servizio Sociale Negli Enti Locali," Bergamo, January 24-25, 1959. (Pp. 275. L. 2,000.) Rome: Istituto di Medicina Sociale. 1960.

I Parassiti Intestinali—Gli Elminti. By Professor Ettore Biocca. *Manuali di Divulgazione e di Guide Pratiche, No. 4.* (Pp. 74; illustrated. L. 600.) Rome: Istituto di Medicina Sociale. 1960.

Klinische Chirurgie für die Praxis. Edited by Professor Dr. O. Diebold, Professor Dr. H. Junghanns, and Professor Dr. L. Zukschwerdt. In four volumes, Volume II, Part 1. (Pp. 244; illustrated. DM. 42.) Stuttgart: Georg Thieme Verlag. 1960.

Medical Physics. Edited by Otto Glasser, Ph.D. Volume III. (Pp. 754+lx; illustrated. £9 8s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

Methods in Medical Research. Volume 8. Editor-in-Chief: H. D. Bruner. Governing Board: Irvine H. Page, René J. Dubos, C. N. H. Long, Carl F. Schmidt, David L. Thomson. (Pp. 368+xiv; illustrated. 74s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

Dermatologic Medications. By Marguerite Rush Lerner, M.D., and Aaron Bunsen Lerner, M.D., Ph.D. (Pp. 208. 45s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1960.

Laboratory Technique for the Study of Malaria. By Percy G. Shute, M.B.E., F.R.E.S., and Marjorie E. Maryon, F.R.E.S. (Pp. 86+x; illustrated. 10s. 6d.) London: J. and A. Churchill, Ltd. 1960.

A Practice of General Anaesthesia for Neuro-surgery. By Robert I. W. Ballantine, M.R.C.S., L.R.C.P., D.A., F.F.A. R.C.S. With the collaboration of Ian Jackson, M.R.C.S., L.R.C.P., D.A. (Pp. 152+viii; illustrated. 27s. 6d.) London: J. and A. Churchill, Ltd. 1960.

Deafness. By John Chalmers Ballantyne, F.R.C.S., D.L.O. (Pp. 254+x; illustrated. 25s.) London: J. and A. Churchill, Ltd. 1960.

Medicine for Dental Students. By R. A. Cawson, M.B., B.S., B.D.S., F.D.S. R.C.S.Eng., and R. H. Cutforth, M.D., M.R.C.P. (Pp. 212+vii; illustrated. 25s.) London: J. and A. Churchill, Ltd. 1960.

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CANCER OF THE RECTUM

Performed for the first time by Czerny[1] in 1879, abdomino-perineal excision of the rectum was established as a routine surgical procedure by W. E. Miles[2] in 1908: fifty years later it remains the most common operation for rectal cancer. There has, however, been no lack of progress since Miles's day, and modern trends were well summarized at the symposium on rectal cancer during the Anglo-American Conference on Proctology held at the Royal Society of Medicine last year.[3] Progress has been made in two directions—first by modification and extension of Miles's operation, and secondly by the development of operations designed to preserve the irreplaceably efficient anal sphincter.

Mortality rates have been lowered, not only because of advances in anaesthesia and other ancillary services, but also because of improved surgical technique. Miles's mortality rate[4] of 12% was remarkable, but to-day Naunton Morgan[5] is able to quote a figure of 3.8%, and W. B. Gabriel,[6] who prefers the perineo-abdominal order of performing essentially the same operation, has similar results. Largely because of the greatly improved facilities for training younger surgeons the mortality rate for this operation is now low in hospitals all over the country, and not only in the main teaching centres. Possibly the most important modification was the introduction in 1939 of the combined lithotomy-Trendelenburg position by O. V. Lloyd-Davies,[7] who has recently reviewed its advantages.[8] The position enables the completion of the abdominal and perineal stages without change of position, making the operation safer, and also permits the combined approach by two surgeons working simultaneously. This procedure has increased the resectability rate, which has risen from 60% to 90% in the last twenty years. The lithotomy-Trendelenburg position is also convenient for restorative operations. Other modern modifications of Miles's original operation include the introduction of high ligature of the inferior mesenteric artery at its origin[9] and improvements in colostomy technique. R. J. Crider and B. L. Neubeiser[10] popularized the immediate establishment of a skin-level colostomy, which is now standard practice, and the placing of the colostomy has also been under review. H. R. Thompson[11] recommends a medially placed stoma which obviates the need for closing the "lateral space," or the same objective may be achieved by routing the colon extra-peritoneally to its more orthodox iliac opening.

The results of the operation, as measured in terms of apparent cure after five years, are among the best in cancer surgery. For all cases the five-year cure rate is just over 50% in many centres, and when the growth is confined to the rectal wall the figure rises to more than 80%. Good as the results of this type of operation have been, dislike of the inevitable colostomy has caused surgeons to reinvestigate the possibilities of conserving the anal sphincter, without prejudice to the operative mortality and morbidity and without sacrificing chance of cure. Naunton Morgan[5] has been a strong advocate of anterior resection, and justifies its use in suitable cases: mortality and morbidity are as low as with combined resection, and the five-year cure rate, in his hands, has been slightly better. He emphasizes that anterior resection must be used only in selected cases—when the growth is situated not less than 10 cm. from the anus and is above the peritoneal floor; when the growth is not anaplastic or too advanced; and when the patient's build permits the satisfactory performance of the operation (it may be impossible in very fat patients, especially in men whose pelvis is narrow). The present-day practice of rectal irrigation with 1:500 perchloride of mercury has greatly reduced the incidence of recurrence at the suture line.

On the other side of the Atlantic the "pull-through" type of sphincter-saving operation has been more popular. H. E. Bacon[12] has described his experiences over the last eighteen years and reports a 3.9% mortality and a five-year cure rate of 55.1%—very similar to the results of anterior resection. In Bacon's series of 656 patients, all but three were continent, although half used enemas regularly.

[1] Cited by Maingot, R., in *Abdominal Operations*, 1955, London, p. 1366.
[2] Miles, W. E., *Lancet*, 1908, **2**, 1812.
[3] *Proc. roy. Soc. Med.*, 1959, **52**, Supplement.
[4] Dodd, H., ibid., 1959, p. 32.
[5] Morgan, C. N., ibid., 1959, p. 41.
[6] Gabriel, W. B., in *Abdominal Operations* (Ed. R. Maingot), 1955, London, p. 1388.
[7] Lloyd-Davies, O. V., *Lancet*, 1939, **2**, 74.
[8] —— *Proc. roy. Soc. Med.*, 1959, **52**, Supplement, p. 40.
[9] Goligher, J. C., *Brit. J. Surg.*, 1954, **41**, 351.
[10] Crider, R. J., and Neubeiser, B. L., *J. Mo. med. Ass.*, 1951, **48**, 365.
[11] Thompson, H. R., *Proc. roy. Soc. Med.*, 1959, **52**, Supplement, p. 49.
[12] Bacon, H. E., ibid., 1959, p. 33.
[13] Goligher, J. C., ibid., 1959, p. 73.
[14] Todd, I. P., ibid., 1959, p. 68.
[15] Wass, S. H., ibid., 1959, p. 51.
[16] Brunschwig, A., and Greenman, R. B., *Surgery*, 1959, **45**, 240.
[17] Ceulemans, G., *Proc. roy. Soc. Med.*, 1959, **52**, Supplement, p. 47.
[18] Fansler, W. A., ibid., 1959, p. 43.

Other surgeons have been less successful so far as continence is concerned. J. C. Goligher[13] reports that all his patients (admittedly few) treated by the pull-through method have been incontinent, whereas 98% of those who had had an anterior resection possessed full control. True continence after a pull-through operation is a matter of chance: as I. P. Todd[14] has shown, one important factor is adequate rectal sensation, for which 5–7 cm. of intact rectal and anal mucosa are essential. It seems likely that the more predictable anterior resection will eventually oust other sphincter-saving operations.

The poor-risk patient and the advanced case pose other problems. S. H. Wass[15] points out that the interests of aged and ill patients, with intercurrent diseases, may best be served by the selection of lesser operations, such as perineal resection for low growths, or Hartmann's operation for high growths: although nowadays out of favour, these operations may be survived by patients unable to stand combined excision or anterior resection. The treatment of the patient with an advanced growth involving the other pelvic viscera is perhaps a matter of philosophy as well as surgery. In the past, A. Brunschwig[16] has favoured complete pelvic clearance and the establishment of a "wet colostomy." At the Anglo-American Conference G. Ceulemans[17] discussed the main problem of what to do with the ureters; the uterus in the female is dispensable but the bladder is not. The construction of an ileal bladder is probably the most acceptable solution, but leaves much to be desired. W. A. Fansler,[18] of Minneapolis, questioned whether the continuance of these ultra-radical procedures is justifiable, and many will agree with his considered opinion that "for cancer of the rectum or lower sigmoid an operation which consists of ligation of the inferior mesenteric artery near its source of origin, the removal of the entire mesosigmoid below this point, clearing of the hollow of the sacrum and wide removal of tissues adjacent to the rectum and anal canal will, in most instances, result in as large a percentage of cures as the more radical procedures. . ." The feasibility of heroic operations may not be the best indication for their performance, and surgeons should beware of the *tour-de-force* and not lose sight of the true meaning of a "palliative" operation.

It was evident from the many papers read at the Anglo-American Conference that there is great vitality in this branch of surgery, and most careful thought has gone to the devising of new methods of attack on rectal cancer. It was perhaps surprising that nothing was said about early diagnosis, although the effect of the extent of the growth on the survival figures was apparent from the statistics quoted. To recommend more use of the sigmoidoscope to proctologists would be redundant, but the importance of this method of investigation needs to be recognized by all. Digital examination of the rectum and sigmoidoscopy should be the rule for all cases of rectal bleeding. If they are not insisted upon surgeons will continue to see advanced cases of carcinoma of the rectum which have been treated as "only piles" until the chance of cure has been lost.

ANTIBODY TO PENICILLIN

The first clear proof of the presence of an antibody to penicillin in human blood followed an accidental observation.[1] A blood bank used cells preserved with penicillin for grouping-tests, and a serum was submitted which agglutinated cells of all groups. This serum was then found to agglutinate cells of any group which had been suspended in a solution of penicillin; in order to "sensitize" them a 25% cell suspension had to be suspended in 3,000 units per ml. for 24 hours. In 2,000 further sera 25 more were found possessing this property, but "only a minority" of the patients providing them were said to have shown sensitivity to penicillin.

The study of this antibody was taken up by K. C. Watson and his colleagues,[2] of Durban, who found it in 18 out of 1,200 specimens of serum. In a recent and fuller account of their work[3] this figure is increased to 40 out of 3,000 unselected specimens, and further studies are reported of the mechanism of the reaction between the antibody and penicillin-treated cells, the effect on it of the presence of penicillin and of penicillinase, and the absence of effect of the antibody on the bactericidal action of penicillin. These authors also submitted sera containing the antibody to starch-gel electrophoresis, and in 22 out of 23 specimens the antibody was found in the pre-albumin zones: in only one was there any in the gamma-globulin. They failed entirely to detect antibody in agar-gel diffusion tests, though precipitation zones in such tests, not only with penicillin but with other antibiotics, have been reported by R. J. Muelling and colleagues.[4] As Watson and his colleagues remark, the fact that these authors waited for up to 21 days for a precipitate to

[1] Ley, A. B., *et al.*, *Science*, 1958, **127**, 1118.
[2] Watson, K. C., Joubert, S. M., and Bennett, M. A. E., *Nature* (*Lond.*), 1959, **183**, 468.
[3] ——, ——, —— *Immunology*, 1960, **3**, 1.
[4] Muelling, R. J., *et al.*, *Amer. J. clin. Path.*, 1958, **29**, 503.
[5] Loiseleur, J., *Ann. Inst. Pasteur.*, 1950, **78**, 1, 151.
[6] Zablocki, B., *et al.*, *Bull. Acad. pol. Sci. Cl.* 2, 1958, **6**, 475.
[7] Josephson, A. F., *J. exp. Med.*, 1960, **111**, 611.
[8] Epp, M., *Science*, 1959, **130**, 1472.

appear casts considerable doubt on its specificity. The relation between this now well-characterized antibody and others which have been reported remains conjectural. Ten years ago J. Loiseleur[5] reported that the serum of animals treated with penicillin contained something which caused an increase in viscosity on the addition of penicillin. B. Zablocki and colleagues[6] have recently confirmed this, and obtained some evidence that the antibody concerned in this reaction interferes with the action of penicillin on bacteria. It is evidently different from the antibody found in human serum, since it fails to agglutinate penicillin-treated cells. A. F. Josephson[7] on the other hand, by vigorous immunization of rabbits, has obtained an antibody which agglutinates penicillin-treated cells but does not interfere with the action of penicillin on bacteria. This was shown by electrophoresis to migrate with the fast gamma- and beta-globulin fractions. Perhaps the most important question in the whole of this subject is whether an antibody in human serum is concerned in either of the two distinct clinical types of sensitivity to penicillin, manifested respectively by rashes developing in some hours and shock developing in a few minutes. M. Epp[8] coupled penicillin T or V (why G was not used is unexplained) to human group O cells, and found that these were agglutinated by the serum of 9 out of 20 patients "with reported allergic manifestations to penicillin." On the other hand, Watson and his colleagues aver that none of the subjects from whom they obtained serum containing antibody gave any history of sensitivity reactions; indeed, most of them were receiving penicillin in large doses and presumably with no ill effects when the serum was obtained. As might be expected in view of this, attempts at passive transfer of sensitivity with serum containing antibody failed. Moreover, they obtained serum "from a number of individuals with well-established drug hypersensitivity to penicillin" and in no case was the agglutinating antibody present. These unequivocal findings seem to mean that this antibody is no more than a curiosity, and that the basis of sensitivity to penicillin must be sought elsewhere.

HEALTH AT WORK

The development of industrial health services in Britain—still a leading country in industrial development generally—has been surprisingly slow. Official policy has completely separated them from the National Health Service, but many industrialists in both private and nationalized sectors have found it worth while to develop their own schemes. At present some 400 doctors are employed by industry in a full-time capacity; an unknown number, certainly not less than two thousand, work in industry on a part-time basis. It is an interesting and rewarding task: upon a good clinical background must be grafted a knowledge of environmental hygiene, of the working processes, and of factory life in general. The newcomer to industry is wise to attend one of the available courses in industrial medicine, such as those at Manchester University and the London School of Hygiene.

Those who work in this field saw with satisfaction the Minister of Labour put his hand to the tiller when he appointed his Industrial Health Advisory Committee in 1955. The committee has advised on the conduct of two surveys of existing industrial health services and working conditions—in the town of Halifax and in the potteries industry. But apart from these fact-finding investigations, there appeared to be little evidence that, as feared by some, the work of this committee had not joined others in the doldrums.

There are two great gaps in the industrial health services of this country to-day. The great majority of factories employ fewer than 250 people, and for these, apart from one or two groups, there is little, if any, special provision: it has so far been in the larger factories and organizations that industrial health services have proved their value. Secondly, there is a lack of industrial hygiene laboratory facilities,[1] which at present exist in an early stage of development only at Manchester, Slough, and Newcastle. Both these deficiencies are being remedied in a number of other countries, and Britain is in danger of falling behind here. Industrial hygiene laboratory services undertake routine chemical, physical, and biological tests to detect and measure hazards in the working environment, such as noxious fumes or dusts, and to detect changes in workers arising from unhealthy working conditions. A recent survey conducted by the Association of Industrial Medical Officers[2] showed that, of 378 practising members of the association who replied to a questionary, no fewer than 232 wanted help from a laboratory to undertake biological tests of workers, and 225 said they needed help with routine investigations of the working environment.

A recent announcement by the Minister of Labour[3] will therefore be welcomed with enthusiasm: the Nuffield Foundation has decided to allocate £250,000 for the further development of grouped industrial

[1] Mathew, G. G., *Brit. med. J., Suppl.*, 1960, **2**, 58.
[2] Schilling, R. S. F., Raffle, P. A. B., and Cooper, J., ibid., 1960, **2**, 35.
[3] *Hansard*, Monday, July 25, 1960.

health services and occupational hygiene laboratories. The money will be applied to assist practical schemes which promise to be self-supporting after an initial period of development. The Nuffield Foundation and the Nuffield Provincial Hospitals Trust have previously made considerable grants for the promotion of industrial health. These include the sponsorship of the grouped medical services provided by the Slough and Harlow industrial health schemes, and of the occupational hygiene and other facilities provided by the Department of Occupational Health in Manchester University, the Slough Occupational Hygiene Service, and the North of England Industrial Health Advisory Service.

It is understood that some of the new grant will be applied to the development of industrial health schemes in older areas and where there are scattered factories. But why only in factories? Industrial health services should cover all places of employment. It is to be hoped that the part of the grant which is to be used for the development of occupational hygiene laboratory services will be directed towards strengthening the existing services at Manchester, Slough, and Newcastle, all of which have been bravely established in the face of much difficulty; a measure of financial assistance will enable them so to develop that industry can adequately test the services they set out to provide. On this their ultimate future will depend. It is good to see the Minister of Labour hand in hand with Lord Nuffield's representatives in this project, which will provide a considerable stimulus to industrial health services in Britain. If the Minister can persuade his colleagues at the Treasury to show similar confidence in and support for the development of industrial health services, much can be done to safeguard the health of the industrial worker, on whom Britain's prosperity depends.

AN UNUSUAL INFANTILE ENCEPHALOPATHY

In 1951 D. Leigh[1] reported from King's College Hospital, London, the case of an infant of 7 months who died of a clinically undiagnosed neurological disorder of six weeks' duration. The pathological features, unique at that time, comprised widespread bilateral and symmetrical lesions of the brain stem and cord, with certain striking histological similarities of the brain-stem lesions—especially in respect of the prominence of the small blood vessels—to Wernicke's encephalopathy as it occurs in the adult. In 1954 I. Feigin and A. Wolf[2] reported three cases in New York, and R. B. Richter[3] another three from Chicago in 1957, all six in infants and with pathological changes as in Leigh's case. R. M. Norman[4] accepted these seven published cases as constituting an entity of obscure aetiology. Four new cases have now been reported this year from Australia by R. D. K. Reye.[5] In addition to the usual necrotizing foci in the brain stem, and the demyelination of the dorsal columns of the cord, which were a feature of Leigh's case, Reye also found that there was widespread demyelination of the peripheral nerves, a territory which seems to have been neglected previously.

The clinical state common to all the cases was that of a diffuse or widely disseminated brain disease not distinguished in life from other types of infantile polioencephalopathy or from the leucodystrophies, and with no source of disease that could be found elsewhere in the body (if febrile vaccinia in Feigin and Wolf's case 3 and measles closely followed by varicella in Reye's case 4 are accepted as coincidental). Thus from these 11 cases the disorder appears to be confined to infants, the earliest age of onset being at birth, the latest at 2 years, and death having occurred at from 4 months to 4 years of age. All 11 cases showed failure of proper neurological development, dating in some from birth and in others from an initial period of normal development, and all displayed motor and mental deterioration. All 11 had feeding difficulties, if this feature is presumed by inference in Reye's cases 2 and 3. Five of the eleven had impaired pupillary light reflex, four were blind, and four deaf. Nine of the group showed motor weakness, with ataxia in four, hypotonia in four, spasticity in three, increased tendon reflexes in four, and decreased reflexes certainly in two and presumptively in four. Convulsions, present in all of Richter's three cases, were not mentioned in the others. Nystagmus was noted in one and tremor in two of Reye's cases, and he also emphasized the intermittency of attacks of extreme flaccidity. In nearly all, attacks of respiratory difficulty occurred, eventually terminating life, sometimes suddenly. In only two out of the 11 cases are there laboratory data on the cerebrospinal fluid; in both the cell count was normal, while the protein was 30 and 50 mg. per 100 ml. in each of these respectively.

Pathologically, the uniform denominator throughout all 11 cases was a necrotizing, non-haemorrhagic process symmetrically in the mesencephalic tegmentum, pons, and medulla, of even distribution. It was characterized by breakdown of the interstitial tissue of the neural parenchyma, with relative preservation of the cell bodies of the neurons, and also by prominence of the small blood-vessels in the affected parts. Reye's case 3 was unique in showing a strong perivascular lymphocytic cuffing and microglial proliferation. Beyond that, the extent and distribution of the histological changes prove on close scrutiny to vary somewhat throughout

[1] Leigh, D., *J. Neurol. Psychiat.*, 1951, **14**, 216.
[2] Feigin, I., and Wolf, A., *J. Pediat.*, 1954, **45**, 243.
[3] Richter, R. B., *J. Neuropath. exp. Neurol.*, 1957, **16**, 281.
[4] Norman, R. M., in *Neuropathology*, 1958, by J. G. Greenfield, W. Blackwood, W. H. McMenemey, A. Meyer, and R. M. Norman, London.
[5] Reye, R. D. K., *J. Path. Bact.*, 1960, **79**, 165.
[6] Lumsden, C. E., *J. Neuropath. exp. Neurol.*, 1950, **9**, 119.
[7] Campbell, A. C. P., and Russell, W. R., *Quart. J. Med.*, 1941, **10**, 41.
[8] Tanaka, T., *Amer. J. Dis. Child.*, 1934, **47**, 1286.

the group. In Richter's case 1 and in Feigin and Wolf's cases 1 and 2 the necrosis was present only in the brain stem, but in Richter's case 2 there were large symmetrical areas of necrosis in the corpora striata, globi pallidi, thalami, and subthalamic nuclei. Similar lesions in the basal ganglia occurred in all four of Reye's cases, most complete in the putamen in case 1 and in the pallidum in case 2. In both Richter's case 3 and Reye's case 3, parts of the cerebral and cerebellar cortex were also affected, with some multilocular cavitation in Reye's case. Complete demyelination of the proximal portions of the optic nerves and tracts, and of the chiasmata, were present in all of Richter's three cases and demyelination of the optic nerves only was noted in Leigh's case. The clinical features of two of Feigin and Wolf's cases suggested that they were similarly affected, but the optic pathways were spared in the three of Reye's cases in which these were examined. Only in two cases other than in Reye's series were the spinal cords examined. Demyelination of the posterior columns was recorded in one of these (Leigh's) and in all of Reye's four cases, beginning at the lumbar region in three of the latter and at the cervical region in the fourth. Again, as mentioned above, Reye also noted widespread demyelination of the peripheral nerves, previously ignored. However, despite all these variations which emerge from a scrutiny of the protocols of all 11 cases, two constant details attract special attention. First, in all 11 cases the substantia nigra was the seat of extensive symmetrical malacia, while, secondly, in none of the eleven were the mammillary bodies affected, though the grey matter round the walls of the third ventricle was affected in several. These two details constitute important differences from Wernicke's encephalopathy (at least as seen in the adult), for in that condition the mammillary bodies are heavily attacked, but the substantia nigra only exceptionally.

Nothing yet is known of the causation of this disease. Reye's—so far the only—attempts at virus isolation were not successful; neither the clinical nor the pathological signs suggest that this is an infectious disease. There are pitfalls in interpreting too closely the structural changes in the immature brain of the infant, as is well illustrated by the not dissimilar multiple cystic softening of the brain in the newborn discussed by C. E. Lumsden,[6] a disease predominantly of the white matter, which it is now generally agreed has no uniform aetiology; some cases are the result of anoxia, some of phlebothrombosis, and others are related to more hidden causes. Nevertheless, all five authors[1-5] on infantile subacute necrotizing encephalopathy have agreed in regarding it as an entity, and, despite the differences noted above, in thinking that its nearest pathological parallel is Wernicke's encephalopathy. In none of the 11 cases, however, was there necropsy evidence of malnutrition nor was there any reason to suspect it clinically. The two patients given vitamin B did not respond to it.

Unfortunately, in none of the 11 cases have we any data on the blood pyruvate levels; these would have been helpful, because hyperpyruvaemia is to be expected in thiamine deficiency. If we except A. C. P. Campbell and W. R. Russell's[7] case of "Wernicke's encephalopathy" in a child 3½ years old (in which the authors stated that there was nothing to suggest a dietary cause), the only infantile encephalopathy due to thiamine deficiency investigated *post mortem* is the Oriental "breast milk intoxication" described by T. Tanaka,[8] a disease that responds to thiamine therapy. The lesions in this Oriental disease are, as in the adult thiamine-deficiency encephalopathy, haemorrhagic. There are, therefore, serious objections to the view that infantile subacute necrotizing encephalopathy is infantile Wernicke's disease. Nevertheless, the curious connexion between thiamine and the grey nuclei of the brain stem, which Wernicke's encephalopathy illuminates and which applies also in other animal species,[2] gives support to the notion that some error of thiamine metabolism especially active in this region of the brain may somehow also be at work. In this respect it may perhaps be significant that two of the eleven cases were sibs, and it seems possible that infantile deaths from a similar illness occurred among the sibs of one of Richter's and two of Reye's cases. It is tempting, therefore, to suppose that this might be another instance of a disease due to an inherited biochemical defect.

CYANOSIS AND LIVER DISEASE

Liver disease can be the cause of cyanosis. Attention is drawn once again to this interesting state of affairs by a recent paper of J. G. Groth and S. Friedman,[1] who report its occurrence in a 9-year-old patient. The lesion responsible is hepatic cirrhosis, and most of the patients described have been children or young adults. Until recently the cause of this syndrome, which was first described by M. Flückiger in 1884,[2] was not well understood. It had been attributed to the abnormal oxyhaemoglobin dissociation which was present in some cirrhotic patients with cyanosis and to other less likely factors such as an alteration in the physical properties of blood or an alteration in the diffusing properties of the lungs.

In 1956 R. Rydell and F. W. Hoffbauer[3] reported the finding of multiple arteriovenous anastomoses in the lungs of a patient with juvenile cirrhosis, who in addition to having the signs and symptoms of hepatic disease with portal hypertension also showed cyanosis with arterial oxygen desaturation, clubbing of fingers, a bruit over the lung bases, and eventually died in cardiac failure. In life a biopsy of the lung had shown no evidence of the presence of any vascular abnormality in it, and at necropsy the lungs looked macroscopically normal. However, by using a special injection technique the existence of microscopic communications

[1] Groth, J. F., and Friedman, S., *Pediatrics*, 1960, **25**, 63.
[2] Flückiger, M., *Wien. med. Wschr.*, 1884, **34**, 1457.
[3] Rydell, R., and Hoffbauer, F. W., *Amer. J. Med.*, 1956, **21**, 450.
[4] Murray, J. F., Dawson, A. M., and Sherlock, S., ibid., 1958, **24**, 358.
[5] Calabresi, P., and Abelmann, W. H., *J. clin. Invest.*, 1957, **36**, 1257.
[6] Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S., *Circulation*, 1951, **3**, 42.

between the pulmonary arteries and pulmonary veins could be shown. This lesion would therefore adequately explain the reason for cyanosis in patients with liver disease.

A case reported by Sheila Sherlock and her colleagues[4] in 1958 was presumed to have this lesion in the lungs, for these observers showed that in their patient, a young man with cirrhosis, chronic cyanosis, and clubbing, there was no shunting in the heart and pulmonary function was normal. The degree of arterial oxygen saturation was also increased when the patient breathed 100% oxygen.

A further possible cause of chronic cyanosis in patients with liver disease would be the shunting of blood from the portal to the pulmonary venous system. Such shunting has been demonstrated after death in cirrhotic patients by P. Calabresi and W. H. Abelmann,[5] who have studied this problem by injecting contrast medium into the clamped portal vein. Clinically, however, an extensive collateral circulation, as shown by splenic portal venography, can exist without cyanosis, and the most severely cyanosed patients probably depend on the presence of the intrapulmonary vascular abnormality described by Rydell and Hoffbauer for the production of cyanosis.

Why this abnormality should occur in some cirrhotic patients is not known. An analogy has been sought between this type of vascular abnormality in the lungs and the familiar "spider" naevus seen often in large numbers on the skin of patients with cirrhosis. It has been shown that the liver is the site of production of chemical substances producing vasodilatation.[6] Perhaps such a substance may be responsible for opening up abnormal vascular pathways, including the anastomoses found in the lungs. The high cardiac output found in patients with chronic liver disease may be due to a similar chemical mechanism.[4] While we cannot be sure of the mechanism by which cyanosis is produced in the cirrhotic, the mistake must not be made of diagnosing a cardiac lesion to explain this phenomenon. Though it may be impossible to make a diagnosis with certainty in life, cyanosis must be remembered as yet a further example of the abnormal vascular lesions in the cirrhotic.

ENOUGH

The age and size of the patient, the severity of the condition which is being treated, and the known side-effects of a drug are some of the factors which influence clinical decisions on drug-dosage within the range which research and experience have shown to be effective. A. M. Butler and R. H. Richie,[1] have recently reminded us that the dose of a drug which will produce a given pharmacological effect is related more nearly to the surface area of the body than to the weight of the body. (The body surface area is approximately the 0.7 power of the body weight.) They recommend, therefore, that drug doses should be related to square metres of surface area rather than to kilograms (or pounds) of weight, and that similar considerations should apply to the calculation of fluid and dietary requirements.

This interesting suggestion has the attraction that it brings dosage of drugs into line with the other physiological measurements which are more nearly directly related to unit surface area than they are to body weight, and its adoption might well be advantageous in applied pharmacological research. Butler and Richie found that the relationship between the average doses of acetylsalicylic acid (in rheumatic fever), sulphadiazine, digitoxin, thyroid extract, atropine sulphate, and diphenyl hydantoin used in different paediatric clinics—doses presumably based on the cumulative experience of a large number of clinicians—did in fact increase in an approximately linear fashion with increasing body surface area. The range of doses on which each mean value was based was, however, very large. They interpreted these observations as providing objective evidence for their thesis that the deliberate use of unit body weight as a basis for adjusting dosage to size of patient would result in general improvement in therapy.

It is worth remembering that body size is only one of the factors which influence the clinical response to drugs. And the aphorism that "the dose of any drug is 'enough'" remains true, though it requires some quantitation in an age when to-day's drug may be to-morrow's poison or vice versa.

[1] Butler, A. M., and Ritchie, R. H., *New Engl. J. Med.*, 1960, **262**, 903.

MINISTERS OF HEALTH

Mr. Derek Walker-Smith's resignation as Minister of Health caused much regret among those in the medical profession who came into official contact with him. He was always courteous, friendly, and good-humoured, and never more so than when he had to say "No" to those arguing the profession's case. Mr. Walker-Smith piloted the Mental Health Act, 1959, through the House of Commons, and was at last beginning to do something for hospital development. When Mr. Macmillan made up his team after the recent election Mr. Walker-Smith found himself once again Minister of Health, a repetition interpreted as politically unpromising. So his resignation on the eve of a reshuffling of Ministers came as no surprise. Mr. Walker-Smith's many friends in the medical profession regret his departure from office and congratulate him on his baronetcy.

Mr. Enoch Powell (see p. 460), who succeeds him, is no lawyer. A classical scholar at Trinity College, Cambridge, he was appointed professor of Greek in the University of Sydney at the age of 25. After distinguishing himself as a fighting soldier in the recent war he entered politics. With a group of other young Conservatives, which included a former Minister of Health (Mr. Iain Macleod), Mr. Powell was influential in giving direction to Conservative thought. He brings to his new office a formidable equipment of experience and intellectual power.

Drug Treatment of Disease

DRUG TREATMENT OF TUBERCULOSIS

II. TREATMENT OF PATIENTS WITH TUBERCLE BACILLI RESISTANT TO STANDARD CHEMOTHERAPY

BY

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As indicated in the previous article,* treatment of tuberculosis with standard chemotherapy is highly successful provided that the patient's organisms are initially sensitive to the drugs used. It is therefore unethical to carry out large-scale trials of newer drugs on such patients, at least until it has been established that there is some probability that the newer drug will be superior to streptomycin, P.A.S., or isoniazid. Because of this the newer drugs have been investigated on a much smaller scale and usually in patients whose tubercle bacilli are already resistant to standard chemotherapy. There have been ethical and other difficulties in carrying out strictly controlled trials. In consequence the scientific data available on the newer drugs are very much less reliable than those relating to standard chemotherapy.

Newer Chemotherapeutic Agents

Before considering what combinations of drugs to use in patients with tubercle bacilli resistant to one or more of the standard drugs, some of the newer drugs will be listed and brief information given about them. The drugs with the most powerful antituberculous action are probably pyrazinamide and alpha-ethylthio*iso*nicotinamide (1314 or ethionamide), while viomycin, kanamycin, cycloserine, and the tetracycline group have a weaker action.

Pyrazinamide

Pyrazinamide is a relatively powerful antituberculous drug whose administration has two major defects—liver toxicity, which has occasionally proved fatal, and the rapid emergence of drug-resistant organisms. Because of its potential toxicity, it should be used only in hospital, at least initially, and liver function tests should be carried out every two weeks. Should any abnormality be shown by the tests it is wise to stop the drug at least temporarily. It is given orally in a dose of 40 mg./kg./day divided into two equal doses with a maximum of 1.5 g. twice a day.

Pyrazinamide resistance often emerges within six weeks if the drug is given alone. There is good evidence that such resistance is prevented if pyrazinamide is given with isoniazid, provided the patient's organisms are initially sensitive to both drugs. There is less evidence about the value of streptomycin or P.A.S. in this respect, but it is reasonably probable that if they are given in adequate daily dosage they will be effective. Tetracycline drugs, cycloserine, or 1314 (at least in a dose of 0.5 g. daily) may fail to prevent pyrazinamide resistance in a relatively high proportion of severe cases.

1314 (alpha-ethylthio-iso-nicotinamide or ethioniamide)

Although at the time of writing 1314 is available only for research purposes in Great Britian it is likely soon to be on the market. There is no doubt that it is a relatively powerful antituberculous drug. Its major side-effect is nausea, which can be very troublesome. The optimal dose is at present uncertain. It is given orally, and the dosage has varied from 0.25 g. twice daily to 0.5 g. twice daily. Nausea is commoner when a dose of 1 g. daily is used, but it seems possible that a dose as low as 0.5 g. daily may be insufficient to prevent resistance to a companion drug. Suppositories are being investigated. Though resistance develops rapidly when 1314 is given alone, it seems probable that it can be prevented by standard doses of streptomycin, isoniazid, or P.A.S. Combination with tetracycline or cycloserine may result in a fairly high proportion of failures, at least in severe cases. There is less information about viomycin and kanamycin, but neither seems likely to be a successful companion drug. One can summarize by saying that 1314 is certainly a useful drug but its exact place in antituberculous chemotherapy is not yet established.

Viomycin

Viomycin is an antibiotic given by intramuscular injection. It can cause giddiness or deafness and can also give rise to renal damage. Such effects are rare when the drug is given in doses of 1 g. twice a day on two days in the week and are not a serious problem even when a similar dosage is given on three days in the week. It is not a very powerful drug. Organisms resistant to it may emerge if it is given alone, but this can be prevented, or at least deferred for many months, by combining the twice-weekly dosage mentioned above with tetracycline in a dose of 2 g. twice daily. Though there is little detailed evidence, it seems probable that daily cycloserine might equally delay the emergence of viomycin resistance. In the case of other newer drugs, it is more probable that viomycin will in the first place fail to prevent the emergence of resistance to the second drug with the subsequent emergence of resistance to viomycin also. Kanamycin seems likely to be similar in action to viomycin and has similar limitations. There is often cross-resistance between them.

Cycloserine

Cycloserine is a relatively weak drug. It is given orally. With doses of more than 1 g. daily toxic effects have been a serious problem. Psychotic symptoms may occur within a few days of starting treatment, and convulsions have been reported fairly frequently. It has been thought that some patients on the verge of cor pulmonale have been precipitated into cardiac failure. In a dose of 0.5 g. twice daily by the mouth toxic effects have been less common. Lower doses are probably less effective, but it is thought that complications are rarer if treatment is begun with a dose of 0.25 g. twice daily, gradually increasing to a dose of 0.5 g. twice daily over

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a period of up to two weeks. Cycloserine resistance emerges less readily than with some of the other drugs and in our experience has not emerged when the drug was combined with 2 g. tetracycline twice daily. Cycloserine is relatively ineffective in preventing the emergence of resistance to pyrazinamide or to 1314.

Tetracyclines

The tetracycline drugs have only a very weak antituberculous action, but there is evidence to suggest their value when given in the high dosage of 2 g. twice daily in delaying or preventing the emergence of resistance to streptomycin (when this is given twice weekly), isoniazid, viomycin, and perhaps cycloserine. With doses lower than 2 g. twice daily they are much less effective in this respect. Some diarrhoea is quite common in the first couple of weeks of treatment, but usually it then decreases and becomes very much less troublesome. A few patients are unable to tolerate the high dosage necessary.

Drug Combinations in Patients with Tubercle Bacilli Resistant to the Standard Drugs

It must be clear from the foregoing account that most of the newer drugs are more toxic, and often less effective, than streptomycin, P.A.S., or isoniazid. They are also much more expensive. Owing to the ethical problems of testing, we are less informed about them. The following suggestions must be read with these limitations in mind.

The Patient Who Has Had Previous "Doubtful" Chemotherapy

If the patient has had previous chemotherapy it is always possible that his organisms are now drug-resistant, for if he is in need of further treatment it is likely that there has been some error in the original therapy. The presence of drug-resistant bacilli becomes more probable if he is known to have received intermittent streptomycin with daily isoniazid or P.A.S. If he has been treated as an out-patient he may well have failed to take his drugs in the rhythms and doses advised.

It is unwise to start such a patient on all three drugs. If his organisms are already resistant to two of them they may well become resistant to the third also. It is wise to treat him in the first place with some form of "holding" chemotherapy until the results of resistance tests become available in two to three months. Viomycin 2 g. in two divided doses on two days in the week together with tetracycline 2 g. twice daily is a suitable combination. It is not highly effective but it does usually prevent deterioration and allows the patient to hold his own and perhaps even improve. It is also relatively free from risk of toxicity. In such a patient it is of course very important indeed that drug-resistance tests should be carried out on more than one specimen of sputum and that they should be thorough. Any laboratory error may result in the patient losing the use of further drugs.

If the resistance tests show any degree of loss of sensitivity to one of the standard drugs this drug should not be relied on to prevent resistance to a second drug used in combination. It is very likely to fail. It may sometimes be justifiable, if there is only a low or doubtful degree of resistance, to use the drug in question, but only *in addition* to another combination of two or more drugs known to be mutually effective in preventing the emergence of resistant organisms.

The Patient with Tubercle Bacilli Resistant to Streptomycin Only

P.A.S. plus isoniazid should be used. In that case it is wise to use the P.A.S. in a dose of 5 g. of the sodium salt four times daily together with isoniazid 100 mg. twice a day. After three successive negative cultures have been obtained it is justifiable to reduce the dose of P.A.S. to 5 g. twice daily. If the disease is very extensive, it may perhaps be unwise to rely only on P.A.S. plus isoniazid, which may sometimes fail in such cases. It is as well to add a third effective drug such as viomycin or pyrazinamide.

The Patient with Tubercle Bacilli Resistant to P.A.S. Only

In patients under the age of 40 the correct treatment should be 1 g. streptomycin daily combined with 100 mg. isoniazid twice daily; in patients over that age there is a risk of vestibular damage with such a dose of streptomycin, and it may be justifiable to lower this to 0.5 g. or 0.75 g. daily. In a very severe case it is probably wise to accept the risk of vestibular damage and to give the full dose of 1 g., at least for the first few weeks.

The Patient with Organisms Resistant to Isoniazid Only

The patient should be treated with daily streptomycin 1 g. together with sodium P.A.S. 5 g. four times daily. If only 5 or 10 g. P.A.S. is given daily, streptomycin-resistant organisms may emerge in a substantial number of cases, and the organisms are likely to become P.A.S.-resistant later. The problem of streptomycin dosage in older people is similar to that discussed in the previous paragraph.

The Patient Whose Tubercle Bacilli are Resistant to Both Streptomycin and P.A.S.

The combination of pyrazinamide (20 mg./kg. twice daily with a maximum of 1.5 g. twice daily) with isoniazid (100 mg. twice daily) is probably the most powerful. In severe cases the risk of pyrazinamide toxicity should probably be taken. In very mild cases it may be justifiable to use viomycin plus tetracycline. It is possible that a combination of isoniazid plus 1314 may prove as effective and less risky than the pyrazinamide–isoniazid combination already mentioned, but there is not yet sufficient evidence on this point.

The Patient whose Tubercle Bacilli are Resistant to Both P.A.S. and Isoniazid

The combination of streptomycin (1 g. daily) and pyrazinamide in the doses already mentioned may well be the best, though there is not much evidence about the value of streptomycin in preventing pyrazinamide resistance. It may be that streptomycin plus 1314 will prove as effective and less risky, but this is not yet established. If either of these combinations is used, and if the case is a severe one, it may be wise in the present state of our knowledge to add a third drug, such as tetracycline or cycloserine. Alternatively streptomycin may be combined with both pyrazinamide and 1314.

The Patient whose Tubercle Bacilli are Resistant to Both Streptomycin and Isoniazid

It is uncertain whether P.A.S. would be adequate to prevent the development of resistance to pyrazinamide or to 1314. The best treatment would probably be to combine P.A.S. in the highest tolerated doses with pyrazinamide and also to use cycloserine, viomycin, or 1314.

The Patient whose Organisms are Resistant to Streptomycin, P.A.S., and Isoniazid

Such patients present a formidable problem, and no drug combination so far tested can give a guarantee of arrest of the disease and permanent conversion of the sputum to negative. Viomycin plus tetracycline may sometimes succeed in making those with milder disease fit for surgical operation, but it is unlikely to achieve sputum conversion on its own. Cycloserine plus tetracycline has similar limitations, in addition to the risk of toxicity from cycloserine. There have been a number of failures, with the emergence of drug resistance, on combinations of cycloserine plus pyrazinamide, cycloserine plus 1314, and pyrazinamide plus 1314. It is possible that the success rate can be improved by using three drugs in combination. Pyrazinamide together with 1314, if possible 0.5 g. twice daily, and viomycin 2 g., twice or three times weekly, may well be the best combination, though there is inadequate evidence regarding it. Cycloserine is perhaps best avoided as the third drug in order to reduce the number of pills which the patient may have to take and to avoid adding the toxicity of cycloserine to that of 1314 and pyrazinamide.

Drug Cover for Surgery

It must be clear from the foregoing paragraphs that none of the therapeutic combinations recommended are likely to be as effective as the standard drug combinations. In addition, patients with resistant organisms often have chronic and extensive disease. The probability of failure of chemotherapy and the emergence of drug resistance is therefore relatively high. In such patients resectional surgery, if it is feasible, is often indicated. The best time to carry this out in the individual case is a matter of judgment. In general, after three months' chemotherapy the patient's bacterial population will have been considerably reduced. If the sputum has become consistently less positive, even though negative cultures have not yet been obtained, it may provisionally be assumed that the tubercle bacilli are not yet drug-resistant. The chemotherapy in use should therefore be able to prevent infectious complications of the operation. Nevertheless, to be on the safe side it is probably wise to add an additional drug as operation cover. It is seldom possible to remove all the tuberculous disease, so it is very important to continue chemotherapy afterwards. The minimum duration should be one year after the first of a series of consistently negative sputum cultures, but in a severe case and if no drug toxicity emerges it is wise to continue for a total of two years regardless of when the operation was carried out.

Conclusions

The treatment of a patient with drug-resistant organisms is always a difficult matter requiring careful judgment of all the clinical, bacteriological and surgical factors involved. It is essential that the resistance tests, which will determine the chemotherapy used, should be carried out with skill and care and that wherever possible a decision should be based on more than one test. The physician must be capable of critical evaluation of the bacteriological results. The surgeon will often have to be consulted. It may be justifiable to ask him to take bigger risks than would normally be permissible, because the prognosis with chemotherapy alone, especially in the patient whose organisms are resistant to all three of the standard drugs, is so uncertain. Nevertheless, if all concerned, including the patient himself, are prepared to take sufficient trouble, many of these unfortunate people can be salvaged.

NOTE.—References to original work on which some of these recommendations are based may be found in Crofton, J. (1960). *Brit. med. Bull.*, **16**, 550

I am glad to acknowledge my debt to many colleagues, including Drs. P. D'Arcy Hart, the late Dr. Marc Daniels, and Dr. D. A. Mitchison of the Medical Research Council, and, in Edinburgh, Drs. I. W. B. Grant, N. W. Horne, J. D. Ross, Sheila Stewart, F. W. A. Turnbull, A. T. Wallace, and J. Williamson. Most of the Edinburgh research was financed by generous grants from the Royal Victoria Hospital Tuberculosis Trust.

AN APPRAISAL OF PSYCHIATRY IN GENERAL PRACTICE

BY

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The flood of mental illness with which the G.P. has to contend presents problems that are hard to solve. Some observers can see no solution apart from a fundamental change in either the patients or the doctors. In the meantime the immediate problem remains and becomes more pressing—namely, how to help the doctors as they now are to deal with the patients who actually consult them.

Psychotherapy

Strictly speaking, "psychotherapy" should mean all methods of treating the mind, but by custom it refers only to treatment by personal discussion between patient and doctor, and here it is used in this sense. The nature of the discussion and of any guidance and explanation offered to the patient varies widely, as do the duration and frequency of these interviews.

Each school of psychopathology believes in general that only psychotherapy practised within the framework of its own particular set of beliefs can be of real value. However, a non-partisan observer will hardly agree. The value of a frank discussion of one's personal problems and an airing of one's inner feelings has always been recognized. It has often been provided by organized religion, sometimes as part of an act of confession. In our modern secular society it is not surprising that the physician is frequently expected to take over this function, which was previously performed by the priest; it is, however, a function which the physician is often most reluctant to fulfil.

Nevertheless, psychotherapy by G.P.s is finding many strong advocates within the medical profession, particularly since Balint (1957) described his methods of training G.P.s at the Tavistock Clinic. One must admire his achievement of inducing G.P.s to continue to attend weekly seminars over a period of years. On the other hand, he reports that half of them did prematurely stop attending, and it appears from the lengthy case-histories he gives that more than half the patients remained ill despite many hours of work on

most of them. It does not seem that a strong case has been made for the usefulness of seminars of this type.

The present enthusiasm for psychotherapy in general practice is in some ways surprising, for psychotherapy is far from being an innovation, and it is not even a new technique in general practice. As long ago as 1923 Ross gave a clear account of its use in general practice in a book which was revised in 1937 and has been repeatedly reprinted (Ross, 1949). More recently there have been numerous reports on the use of psychotherapy by G.P.s in the National Health Service. I and my colleagues described its use in a practice that had been started in a rehoused community soon after the N.H.S. began (Franklin *et al.*, 1951), and there have been many other similar accounts.

Ten years' experience of psychotherapy in general practice has given me some clear impressions of its value.

A sympathetic ear and a kindness of manner are something which every doctor strives to offer every patient, whatever the illness. But I have found, as one would expect, that psychotherapy as a specific treatment is more effective for some psychiatric disorders than for others ; I have found that the condition which responds best is an anxiety state in a young adult. Once a doctor has dealt as best he can with patients of this type who are on his list, the use of formal psychotherapy becomes fairly infrequent. A great deal of psychiatric illness will remain, however, which is unsuitable for psychotherapy or has not responded to it, and this in my view constitutes the main problem of mental illness in general practice.

For conditions other than an anxiety state psychotherapy may be ineffective and so lead to discouragement of both doctor and patient ; in other cases it may actually be harmful, and it may make the patient worse even to the extent that his life is endangered. Therefore the basic medical discipline must be followed of trying to establish a diagnosis before starting treatment, lest one does harm by inappropriate treatment.

Five Main Groups

In my experience most cases of mental illness encountered in general practice belong to one of five main groups—namely, anxiety states, depression, psychosomatic disorders, schizophrenia, and hysteria. The diagnostic features of these conditions have often been described and will not be repeated here. The brief outline which follows, of how each can be tackled by the G.P., will help in evaluating the role of psychotherapy and of other treatments that are at present possible.

Anxiety State.—In my experience patients either respond quickly to psychotherapy or they scarcely benefit at all. As regards the number of occasions on which the patient should be seen, I have found that a law of diminishing returns operates, and if I have not made much progress after two or three interviews I have rarely made much more after a dozen. I have therefore given up undertaking prolonged courses of psychotherapy and rarely continue for as many as six sessions. To continue indefinitely when little progress is being made does not seem to benefit the patient very much and it may create difficulties for the doctor. If a strong interpersonal relationship develops the patient may become very dependent on the doctor. On the other hand, for a G.P. to end a series of psychotherapeutic interviews is not the equivalent of a hospital doctor's discharging a patient from his care ; a G.P. can never discharge a patient, and the doctor–patient relationship in general practice is virtually permanent. The doctor is always freely available to the patient, and their relationship is constantly developing.

Psychosomatic Disorders.—Although some of these are serious disorders which can kill through the somatic changes they produce, they nevertheless often respond to psychological treatment ; I have found that they can sometimes be helped by psychotherapy, but often a great deal of work seems to produce little reward. I have found that there is another technique which is, fortunately, much more effective,—namely, hypnosis. An account of my use of hypnosis appears elsewhere (Franklin, 1957). It can be used for treatment by direct suggestion and also as an aid to psychotherapy. For example, dysmenorrhoea usually responds to suggestion alone, migraine and many cases of asthma to suggestion and a quite superficial discussion, while a few asthmatics need deeper psychotherapy if the initial response to hypnosis is to be maintained.

Depression.—This is a very common and very distressing condition and is an important killing disease. The number of deaths by suicide is comparable with the number of deaths from road accidents, and depression is the usual cause of suicide. The diagnosis of depression may not be immediately apparent as the patient may present with such symptoms as pains and lassitude. It is important to distinguish depression from anxiety state, which it may resemble, as the treatment of the two conditions is quite different. In my experience depression is scarcely affected by hypnotic suggestion and can be made worse by psychotherapy of any depth. The patient's feelings of guilt and unworthiness can be made worse if he is encouraged to recall unsavoury incidents from his past life, and the risk of suicide may thereby be increased. Psychotherapy should amount to little more than a sympathetic ear and an understanding manner. The principal treatment for depression is, in my view, physical rather than psychological. At present we have a variety of drugs as well as electroplexy, but we still await a completely specific remedy.

Schizophrenia.—This seems to be virtually uninfluenced by psychotherapy, and it is, in any case, difficult to establish a normal relationship with a schizophrenic when the disease is active. It is my opinion that, like depression, it calls primarily for physical methods of treatment. Recently introduced medicaments which have enabled chronic schizophrenics to be reinstated in society are encouraging. It seems that pharmacological and biochemical research may soon lead to a major breakthrough in both schizophrenia and depression.

Hysteria.—I regard hysteria as evidence of a major psychiatric disorder. Psychotherapy is difficult and is best restricted to a discussion of the patient's current problems. Contrary to what is widely believed, its treatment by hypnosis is difficult and potentially dangerous and is best not attempted in general practice. The fewer medicaments that are given, the better. Often the best that can be done is for both patient and doctor to accept the symptoms and not to look for a cure.

Symptom Tolerance

We can at present offer no more than palliative treatment to many of our psychiatric patients. However, we can sometimes help if we explain our limitations to the patient and encourage him to accept his symptoms and to carry on his life despite them. Those who can do so often find that their lives are transformed. Later their symptoms may disappear, possibly because of a remission of their illness, which would have occurred in any case.

There is, however, a hard core composed of psychiatric patients who in the present state of knowledge are virtually untreatable, but who do not need to be confined within a hospital. They are a constant worry to their G.P.s. Many of them have personality characteristics which make them tiresome and unrewarding patients. Even if the G.P. fails to give such patients insight into the nature of their illness he should try to see it in perspective himself. He should no more feel personally responsible for medicine's present inability to relieve these patients than he does for medicine's present inability to relieve many organic disorders. The doctor must learn to tolerate his patients having symptoms which he cannot cure.

Symptom tolerance can be a rewarding exercise for both patient and doctor.

Postgraduate Training

Though psychiatry presents G.P.s with some of their major problems, it was proved difficult to organize helpful refresher courses in it. Seminars of the type already referred to which meet regularly for years to discuss details of psychotherapy and the handling of the doctor–patient relationship have enthusiastic advocates. However, the reported results do not show that this is a method which should be generally adopted, and it is difficult to justify devoting so much time to a single technique.

I think that the following are some of the matters with which G.P. refresher courses could profitably deal.

Diagnosis.—A complete diagnosis is rarely possible in any branch of medicine, but diagnosis must form the basis of rational treatment. It is difficult to agree with Balint (1957) when he dismisses diagnosis as "irrelevant diagnostic tags." Diagnosis is irrelevant only if there is no effective treatment or if all conditions are treated in the same manner.

Therapeutic Techniques.—Instruction is needed in techniques that can be applied in practice, of which two come to mind: first, one of the well-tried methods of brief psychotherapy, and, secondly, hypnosis. G.P.s should have the possibility of becoming acquainted with hypnosis and its capabilities and limitations, even if they do not choose to use it themselves.

Physical Treatments.—All doctors use drugs in treating mental disorders, and most would like to know how far a rational basis for traditional medicaments is possible. One would also be grateful for any guidance through the maze of new drugs and their accompanying glossy promotion literature with which we are becoming surrounded.

Psychological Measurements.—G.P.s would like to know about methods of measuring different traits by such procedures as intelligence tests and personality inventories, and to know how they can be applied clinically.

Research.—Information about research at the growing points in psychiatry is needed, particularly relating to the biochemical studies which seem to be breaking down psychiatry's previous frontiers.

Summary and Conclusions

Mental illness provides one of the main unsolved clinical problems in general practice. Much of it is amenable only to palliative treatment in the present state of knowledge and there is a hard core which is virtually untreatable.

Psychotherapy is a well-tried and valuable technique, but as a specific treatment it is effective in only a minority of cases; training in psychotherapy should form only a small part of postgraduate courses for G.P.s. The G.P. is greatly in need of help in the formidable problem presented by the patients who are not relieved by psychotherapy.

The potentialities of psychotherapy have been adequately explored and reported. There is little need for further descriptive accounts with detailed case-histories. Controlled studies of the value of particular treatments are needed, though they are difficult to carry out.

The next big advance in the management of mental illness in general practice is likely to result from the elaboration of new methods of physical treatment.

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VISION SCREENING OF VERY YOUNG OR HANDICAPPED CHILDREN

BY

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It is now generally agreed that the younger the age at which visual defect is diagnosed and treated the more favourable is the outlook for recovery or improvement of function. Earlier ascertainment depends upon appropriate methods of assessment. For some time I have been interested in the problem of testing the visual acuity of children, especially the very young, the mentally handicapped, the partially sighted, the deaf, those with cerebral palsy, and those with multiple handicaps.

Many years ago, as a result of discovering several school children with high myopia, whose disability had been missed until 8 or 10 years of age, and other children whose severe visual defect had been mistaken for mental backwardness, Dr. Gertrude Pugmire and I came to the conclusion that it was desirable to carry out routine vision-testing of 5-year-old school entrants.

The picture tests then available did not prove satisfactory, especially with retarded children, many of whom found difficulty in relating the black-and-white

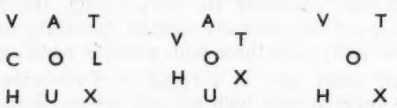
stylized pictures to the solid objects they represented. The E test was given an extensive trial, but, although we found that in our own hands under controlled conditions in clinics it gave better results than the picture charts, we were not satisfied with the results we obtained under less favourable conditions in schools. Many of the school nurses we consulted also admitted to us that they found difficulty in interpreting the young child's responses, especially with the last two lines.

In our experience, there are three main drawbacks to the E test. These also apply to the Sjögren Hand test. (1) Choice is very limited: only the four cardinal positions can usually be employed, since young children find difficulty in coping with diagonals when required to indicate or reproduce the position of the presented symbol with their own hand or with a wooden model. (2) Children under 7 years are often confused between lateral positions, although they rarely confuse up and down; hence, when the child indicates an incorrect lateral position he may not be seeing the letter, he may be merely guessing, or he may be seeing it correctly but is confused in reproducing it. (3) Although the E is measured accurately according to Snellen standards, the pattern presented is constant, so that the test does not give further information regarding the child's ability to discriminate differences in configuration, which it is desirable to have.

Children of 5–7 Years

After prolonged observation of children in infant schools in order to discover which letters they first learned to recognize and to write spontaneously, we designed two charts, one using script and the other block letters. The latter proved the more satisfactory (Pugmire and Sheridan, 1930). This block-letter chart has recently been revised in the light of greater understanding of the psychological principles involved. The final chart contains nine letters selected according to the now well-established fact that the average child can copy a vertical line at 2 years, a horizontal line at 2½ years, a circle at 3 years, a cross at 4 years, and a square and triangle at 5 years. (At 7 years he can copy a diamond.) The nine letters chosen, H L T C O X A V U, are built on these familiar and copyable shapes. The letters are well spaced, with no more than three on any line.

Procedure.—The chart is hung in a good light at the child's eye-level and the reading distance of 20 ft. (6 m.) is accurately measured. One eye is then efficiently occluded. The child is instructed to say the letters to which the examiner points if he knows them; if not, he is shown how to copy them by drawing them in the air with his index finger (Pugmire and Sheridan, 1957).



A, 9 letters. B, 7 letters. C, 5 letters.

FIG. 1.—Key-cards.

Some of our colleagues, while admitting the value of the additional information obtained from personal observation of the child's performance, found this procedure slow for screening purposes, and difficult to interpret when the child drew minutely. To solve this difficulty a nine-letter key-card was designed (Fig. 1A). This is given to the child, and he is asked to "point to the letter on his card which is the same as the one the examiner is pointing to on the chart." This procedure provides an easy, rapid, and interesting screening test for normal children of 5–7 years and for handicapped children of similar mental level. The result of routine testing by 15 different examiners of a total of 1,552 5-year-old school entrants has recently confirmed our experience that the normal vision of 5-year-olds should be regarded as R. 6/6 and L. 6/6 (Pugmire and Sheridan, 1960). Inability to see 6/9 in one or both eyes constitutes a visual defect. The chart is not suitable for normal children over 7 years, who need more difficult material. Incidentally, the letters on the key-card correspond to Snellen 6/9 so that this card itself can be used as a screening device for older children in an emergency.

[*Note.*—Some immature children in this age group find it difficult to maintain rapport with the examiner at 20 ft. (6 m.). For these children the modified procedure described below can usefully be employed.]

Children of 3–5 Years

In connexion with a further piece of personal research I found it necessary to devise a means of testing the visual acuity of pre-school children, normal and handicapped. Study of the literature was unhelpful. Apart from the E, Hand and picture chart tests the only other test mentioned for very young children was Worth's balls. I have never seen the material for this test, and when, from a study of the descriptions available, I assembled a set of balls of various sizes and tried out a version of my own, I found the testing situation difficult to control and the results impossible to assess. I was therefore obliged to evolve new procedures. Three sets of material were considered to possess promising potentialities—single-letter cards, wooden blocks in different shapes and sizes, and miniature toys. The first and last have now been given extensive trials. The shaped blocks are still under investigation.

Letter Cards

In testing children under 5 years three important findings emerged. (1) Most of them found it difficult to maintain rapport with the examiner at the full 20 ft. (6 m.) for the entire duration of the test. (2) They responded more satisfactorily when presented with single-letter cards measuring 5 by 5 in. (12.5 by 12.5 cm.) than with the whole chart. (3) Although the children were unable to *copy* the nine letters before 5 years, they could *match* them at a younger age. One obvious solution was to test in a mirror at 10 ft. (3 m.) which entailed discarding two letters, C and L, of the original chart, and preparing a key-card of the remaining seven "square" letters (Fig. 1 B). The child and the examiner sat side-by-side facing the mirror. The examiner then held up the card above or beside the child's head so that he was obliged to look into the mirror in order to see it. In practice this worked satisfactorily, but in schools and nurseries it was not always possible to obtain a mirror of suitable size and position. I therefore decided to present the original single-letter cards at 10 ft. (3 m.) and to add two extra letters corresponding in dimensions to the 6/4 line, giving the equivalent of 6/8 at 10 ft. The full complement of the letters used was thus: 6/60 O; 6/36 X; 6/24 V; 6/18 A, T; 6/12 U, X; 6/9 H, T; 6/6 O, X; 6/4 T, V. This was considered and in practice proved to be a

sufficiently refined screening test. The average child of four years is quite capable of matching all seven selected letters. Similarly, the majority of 3-year-olds were found to be capable of matching the five simpler letter shapes, T, H, O, V, and X at 10 ft. A few 2-year-olds can do this test, but some confuse V and X. In this case, X can be covered, which still gives a choice of four differently shaped letters (Fig. 1, C).

Procedure.—The child is given the appropriate key-card. The examiner then shows his own big O, saying: "I've got one like this and you have got one. Show me yours . . . Good." If necessary—for example, with the deaf or mentally handicapped—the examiner can take the child's hand and place his index finger on the correct letter. When the examiner is satisfied that the child understands the procedure, one eye is covered (an ordinary plastic shade is suitable provided it fits) and the test is carried out for right and left eyes separately at 10 ft. At least one letter of each size is presented down to line 12 and thereafter both letters for lines 6 and 4. A good light is essential, and the card must be presented at the child's eye-level. A little preliminary coaching at home or in the nursery school will improve performance and cut down the time needed for each child.

Standards.—This procedure can be used with all normally intelligent children of 4 years (seven letters), with approximately 80% of 3-year-olds (five letters), and with about 30% of 2-year-olds (four or five letters). The child with normal vision may be expected to match down to the smallest letters, with each eye separately. If he cannot match the two final letters—that is, the equivalent of 6/8—it is advisable to retest within six months. If he falters on the two "6" letters—that is, the equivalent of 6/12—it is safer to refer him immediately for an expert opinion. Any child with squint or history of squint should be referred to a consultant whether or not the vision is normal.

Near Test.—Although some ophthalmologists consider it is unnecessary (Ingram, 1960) I was anxious to find some means of testing the near vision for two reasons: (1) to discover whether the child with poor distant vision could see well or badly close by, and (2) to be able to record the recovery of vision in an amblyopic eye when the good eye is occluded. Experience has taught me that in the course of normal development the child's "spatial world"—that is, his field of continuous visual and auditory attention—gradually expands from within a few inches distance from his eyes and ears at 5–6 weeks to full adult range by 5–6 years. Moreover, I have found, as Guibor (1959) has also recently suggested, that in the treatment of amblyopia the near vision often shows signs of recovery before the distant vision. A suitable card of graduated block capital letters, measured as closely as possible to standard N sizes, was therefore prepared. This has proved useful not only for young children but also for older non-speaking or illiterate children. The same matching procedure is used.

Test With Miniature Toys (1½–3 Years)

This test was first evolved for use with severely handicapped children and especially for those whose opportunities to learn from experience had been limited and who were not only unable to match single letters but were also unable to name or match coloured pictures pasted singly on 5 by 5-in. (12.5 by 12.5-cm.) cards. Fortunately most of them had experience of playing with toy motor-cars, aeroplanes, dolls, wooden blocks, balls, and various domestic objects. I therefore decided to investigate the possibilities of using miniature models of these. The results were promising. The toys eventually selected were car, plane, doll, chair, knife, fork, spoon. In order to discover the approximate mental age required, the test was then tried out with normal day-nursery children, who co-operated with gratifying enthusiasm. It proved suitable for application from about 20 months up to the age when the letter cards could be applied. Testing procedures suitable for still younger children are under investigation.

Procedure.—The examiner asks the child at conversation distance to name the toys shown. With normal children even the youngest usually know the car, doll, chair, and spoon. The majority of those over two years can cope with all seven toys. Having confirmed that the child understands the procedure, the examiner withdraws to 10 ft. (3 m.) and, presenting one of the toys, asks the child: "What's this?" It is important that the toy should stand out clearly against its background. I usually place it on a strip of black velvet. If the child cannot speak intelligibly he is given a duplicate set of toys and requested, by signs if necessary, to indicate the one which is the same as the one the examiner has presented. In this case the examiner's and the child's car, chair, and doll's dress should be of different colours or the child may make the more primitive match by colour rather than form. Whenever possible two sizes of miniature knife, fork, and spoon are used. The difference between the smaller fork and spoon calls for very fine visual discrimination. The test should be given with each eye separately. If the child will not tolerate the plastic shade it may be possible to persuade him to look through a 1-in. (2.5-cm.) hole in a highwayman's cloth mask. The near vision can be tested by asking him to pick up small sweets, crumbs, pieces of thread, or "pills" of cotton wool.

Although it has not been possible to determine the precise relationship between the miniature toys and the Snellen letters, this test has proved clinically useful not only in establishing that the child can see small objects at 10 ft. but also in demonstrating the difference in visual acuity between the right and left eyes. The need for early detection of amblyopia in young children has been stressed by Cole (1959). It is important that the medical examiner himself should observe how the child behaves in the test situation, since the manner of his performance is often as revealing as the final result, perhaps more revealing. Hence these tests are not intended for large-scale routine screening by ancillary personnel.

In order to give valid results it is essential to observe the following conditions: the distance should be measured accurately; the toys described should be used; the eye not under test should be properly occluded; the examiner should be experienced in the handling of young children; the child should be given as much explanation of the "games" as is within his understanding; and the mother or other familiar adult should be in attendance.

Children "At Risk."—Although it is impracticable to apply vision screening tests to all infants and young children, follow-up of certain groups "at risk" of visual disability is desirable. These include the children of mothers who have suffered from rubella, toxoplasmosis, or toxaemia during their pregnancy; babies who have experienced premature, prolonged, or difficult birth,

especially those to whom oxygen has been administered in the neonatal period; children with cerebral palsy, galactosaemia, or lipoid diseases; deaf children; mentally retarded children; children with myopia or other serious visual defect in the family; and all those with squint or a history of squint.

Summary

A graded series of simple clinical vision tests which have proved useful for young children and children with various physical and mental handicaps is described.

Two sorts of material were used according to the age and ability of the child—that is, Snellen letters and miniature toys.

Children of 5–7 years (and handicapped children of corresponding mental level) were tested with a specially designed chart at 20 ft. (6 m.). It was found that normal vision at this age is R. 6/6, L. 6/6.

Children of 3–5 years were tested with single-letter cards at 10 ft. (3 m.). It was found that normal vision at this age approximates R. 6/8, L. 6/8.

Children of 1½–3 years were tested with seven miniature toys. The test proved clinically useful in demonstrating visual acuity for small objects at 10 ft. (3 m.) and in detecting differences in functional ability between the right and left eyes.

The help given by Dr. G. E. Pugmire in the preparation of this paper and in the investigations which preceded it is gratefully acknowledged.

The material for these tests can be obtained from the National Foundation for Educational Research, 79, Wimpole Street, London, W.1.

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MATERNAL DEATHS IN ENGLAND AND WALES, 1955–7

MINISTRY REPORT ON CONFIDENTIAL INQUIRIES

The second report on "Confidential Enquiries into Maternal Deaths in England and Wales," which covers the period 1955–7, was issued last week by the Ministry of Health as No. 103 in its series *Reports on Public Health and Medical Subjects* (H.M.S.O., London, price 4s. net). This report, of which the *Journal* received an advance proof, was the subject of editorial comment in our issue for July 9 (p. 123). Here, the main findings are summarized. The first report on maternal deaths (No. 97 in the Ministry's series), with whose findings those in the present report are compared, was issued in 1957 and covered the years 1952–4. The second report is by Mr. Arnold Walker, F.R.C.O.G., Mr. A. J. Wrigley, F.R.C.O.G., Dr. G. S. W. Organe, F.F.A. R.C.S., Dr. Roma N. Chamberlain, and Dr. W. J. Martin, D.Sc. The method of inquiry was the same as in the first series.

Plan of Report

After a short introductory chapter the findings in nine major causes of maternal death are analysed. There is then a section on the 1957 Asian influenza epidemic and maternal mortality. Finally, the "avoidable factors" in the antenatal period, during labour, and during the puerperium are discussed, and the report ends with a note on prevention. Tabular data are given as an appendix. The nine major causes of maternal death discussed in the report are: (1) Toxaemia of pregnancy, (2) haemorrhage, (3) pulmonary embolism, (4) abortion, (5) cardiac disease associated with pregnancy, (6) caesarean section, (7) deaths due to complications of anaesthesia, (8) sudden death in labour, and (9) rupture of the uterus.

During the period reviewed there were 2,149,396 births and 1,112 maternal deaths directly due to pregnancy and childbirth. Of these deaths, 861 were the subject of inquiry. In addition, 339 out of 368 "associated deaths" (deaths due to disease occurring in pregnancy or childbirth) were inquired into. Since the previous series there has been a fall from 43.1 to 40.9% in the proportion of deaths with avoidable factors due directly to pregnancy and childbirth. This is ascribed mainly to a "remarkable fall" in the number of deaths from post-partum haemorrhage with retained placenta.

The total number of maternal deaths directly due to pregnancy and childbirth in the years 1955–7, both those recorded by the Registrar-General and those here reported upon, fell by about one-fifth compared with the years 1952–4, despite an increase in the total births from 2,079,275 to 2,149,376. A fall of this order occurred among all causes of maternal death with the exception of haemorrhage, pulmonary embolism, and sepsis. Deaths from haemorrhage showed a greater fall, while deaths from pulmonary embolism and sepsis remained much the same. If the deaths due to pregnancy and childbirth were arranged in clinical groups the four largest groups had undergone some change in their relative importance as compared with the 1952–4 series as follows:

	Number of deaths		*Percentage of total deaths*	
	1952–4	1955–7	1952–4	1955–7
Deaths due to toxaemia (including toxaemic accidental haemorrhage)	246	188	22	22
Deaths due to haemorrhage (excluding toxaemic accidental haemorrhage)	188	121	17	14
Deaths due to abortion	153	141	14	16
Deaths due to pulmonary embolism	138	147	13	17

Toxaemia of Pregnancy

In 1955–7 toxaemia of pregnancy still remained the most important cause of death in childbirth, accounting for just over one-fifth of the deaths directly due to pregnancy and childbirth. There were 188 such deaths, compared with 246 in the 1952–4 series. Of these, 46 women died undelivered, four miscarried, 67 had stillbirths, 60 had live births, and 11 had twins. This was a much higher proportion of twins than among all births. The proportion of cases with avoidable factors had risen from 52% in 1952–4 to 54.8%.

Faulty antenatal care was by far the most serious and most frequent avoidable factor, states the report, and the faults recorded in this series would be regarded by most doctors as inexcusable in these days. Greater emphasis and wider appreciation must be given to the vital importance of selection of cases for hospital confinement. No doctor or midwife should ever willingly agree to confinement out of hospital for women in the older age-groups, who might have borne more than four children previously, and especially when previous pregnancies had been complicated by pre-eclamptic toxaemia. Shortage of hospital beds did not seem to provide an avoidable factor in this series, but it would not be possible to say whether indirectly it contributed to the death of these women.

Haemorrhage

There were 138 deaths from haemorrhage, of which 72 (52.2%) had avoidable factors. This compared with 220

deaths in 1952 to 1954, of which 135 (61.4%) had avoidable factors. There was a remarkable drop in the number of deaths from post-partum haemorrhage with retained placenta, and a large but less impressive fall in the number of deaths from other post-partum haemorrhage. This was probably due to an improved standard of management of the third stage of labour and greater use of the flying squads. The increasing use of ergometrine as a prophylactic against the occurrence of haemorrhage might well have played a part.

Number of Deaths in Each Clinical Group and the Number in Which Avoidable Factors Were Considered to be Present

	Number of Deaths	Deaths with Avoidable Factors	
		Number	%
Accidental haemorrhage, toxaemic and non-toxaemic	40	23	57·5
Placenta praevia	28	12	42·9
Post-partum haemorrhage with retained placenta	24	14	58·3
Other post-partum haemorrhage	46	23	50·0
Total	138	72	52·2

In only 39 out of 138 deaths from haemorrhage was a haemoglobin estimation recorded, and the report stresses the importance of the diagnosis and treatment of pre-existing anaemia. Lack of appreciation of the seriousness of the condition still remained the primary avoidable factor in cases of haemorrhage. In hospital, blood transfusions were not started early enough and junior medical officers failed to obtain consultant help. In domiciliary practice there was delay in summoning flying squads, sometimes because the midwife attempted to summon the doctor first. Failure to select for hospital confinement the grand multiparae or cases with previous histories of third-stage complications and multiple pregnancies was still a contributory factor in the death of these patients.

Pulmonary Embolism

Compared with 138 cases in 1952–4, there were 147 deaths due to pulmonary embolism in the 1955–7 series, and in addition a further 10 cases in deaths considered to be associated with pregnancy. Of these 157 cases, 17 occurred during pregnancy, 114 followed vaginal delivery, and 26 followed caesarean section.

In those cases where a thrombosis or other warning sign was detected death occurred less commonly within 14 days of delivery than when the thrombosis was unsuspected. Haemoglobin estimations during pregnancy were recorded in 33 out of 140 cases, and there was evidence of anaemia in only 19.

Abortion

Owing to the unreliability of the figures, comparisons are not made between deaths from abortion in 1952–4 (given as 153) with those in the present series.

Of the 141 deaths from abortion in 1955–7, 91 were recorded as avoidable in that the abortion was procured for non-therapeutic reasons. Of these 91 the abortion was done by the woman herself on 40 occasions, by some other person in 20, and in the remainder the person responsible was unknown. In 53 of these cases the woman was married.

In these cases of procured abortion in which the patient's circumstances were noted in the reports, many of the married women were reported to be living in poor circumstances and some had families of considerable size. Most of the single women were recorded as living in comfortable circumstances.

Death from air embolus was always preceded by a method of procuring abortion which involved the injection of some fluid under pressure.

Cardiac Disease Associated with Pregnancy

There were 102 deaths from cardiac disease complicating pregnancy, compared with 121 in the 1952–4 inquiry. In these 102 cases, in at least 40 instances (39.2%) an avoidable factor was considered to be present. In the 62 cases where no avoidable factor was present, death from sudden acute heart failure occurred more frequently during pregnancy than during labour or in the puerperium. In the group of 40 cases where avoidable factors were thought to be present a higher proportion died during labour.

Time of Death in Relation to Confinement

	Number	%
Died in pregnancy	51	50·0
Died in labour	14	13·7
Died within 24 hours of completion of labour	10	9·8
Died in puerperium (excluding the first 24 hours)	18	17·6
Died following caesarean section	9	8·8
Total	102	99·9

The nature of the cardiac lesion was rheumatic heart disease in 89, coronary artery disease in 5, bacterial endocarditis in 5, and other in 3. Among the 102 deaths from cardiac disease there were 19 cases which did not receive any hospital care.

The danger of the operation of caesarean section in pregnant women suffering from cardiac disease would appear to have been confirmed, states the report.

Caesarean Section

A survey was made of 180 deaths following caesarean section. The calculated maternal mortality rate following caesarean section for the country as a whole was probably about 3.5 per 1,000 deliveries by this method.

The presence of avoidable factors where directly associated with the performance of the operation would appear to be limited in the main to its employment in the treatment of placenta praevia, obstructed labour, and valvular disease of the heart. In patients suffering from pre-eclamptic toxaemia and eclampsia the avoidable factor did not appear to be concerned with the operation, but almost entirely with such matters as deficient antenatal care or unwise arrangements for the confinement. Relatively few avoidable factors were apparent in the small number of deaths that followed the performance of a premeditated and prearranged operation.

Genuine and serious obstructed labour must be becoming progressively more rare as each year passed. Therefore each case when it occurred demanded the most skilful attention available. If the confinement took place in the patient's own home, or in a small maternity home, the diagnosis indicated an immediate call for skilled assistance but not necessarily the transference of the patient to hospital. Only after the most careful consideration should caesarean section be performed on patients suffering from cardiac disease.

From the records of the present series of cases it was still abundantly evident, states the report, that the operation was performed on many occasions before every effort had been made to restore the general condition of the patient. This was especially so in the case of some patients who suffered from ante-partum haemorrhage.

Deaths Due to Complications of Anaesthesia

Deaths due to complications of anaesthesia showed a progressive reduction since the previous report.

Annual Deaths ("Avoidable" Deaths in Parentheses)

Year	1952	1953	1954	1955	1956	1957
Deaths	15	15	19	12(11)	11(8)	8(5)

Inhalation of stomach contents occurred in 18 of the 31 deaths recorded in 1955–7, and in 17 of these was the major cause of death. In five, and possibly six, cases the anaesthetic was administered by the single-handed obstetrician. On the latter the report comments: "There can be very few obstetric emergencies whose urgency justifies this practice."

The case records suggested that many of these tragedies could have been avoided by a more experienced anaesthetist. A consultant anaesthetist should be responsible for anaesthesia in the obstetric department, for the instruction of his juniors, and should be available for consultation by them in any case of difficulty.

Sudden Death in Labour

Excluding cases of pulmonary embolism, sudden death in labour occurred on 44 occasions in the 1955–7 series. The causes were as follows: obstetric shock 17, amniotic embolus 11, air embolus 9, and various 7.

Consideration of the few avoidable factors present in this series brought to light no fault that had not been fully considered elsewhere. If such avoidable factors were present, they could have been avoided by the application of common knowledge to not unusual circumstances, or by promptly sending for assistance. Too often, also, a post-mortem examination tended to lose value by not being specifically directed to obstetrical features of the case.

Rupture of the Uterus

Rupture of the uterus occurred on 33 occasions and was thought in every case to have accounted for the death of the woman. Some other cases might have remained undiagnosed and death been ascribed to another cause such as post-partum haemorrhage.

The majority of ruptures were associated with obstructed labour or extensive intrauterine manipulations. In four instances rupture occurred in the scar of a previous caesarean section. In three instances rupture was associated with the use of oxytocic drugs.

The high incidence associated with older women and with multiparity emphasized once more the vital importance of the making of appropriate arrangements for the confinement. The fatal result in some of these cases would probably have been avoided by correct booking and by seeking a consultant's opinion, both in domiciliary and hospital cases, at a much earlier time in labour.

Asian Influenza, 1957

Twenty cases of death from Asian influenza associated with childbirth and pregnancy were reported during the epidemic of September to November, 1957. Eight further cases were recorded on the death certificates, but were missing from the inquiry.

There was an increased death-rate from Asian influenza if the patient was near term or in labour. Special care seemed to be needed for those patients with even mild mitral stenosis who contracted Asian influenza.

The Avoidable Factors

Of the 861 deaths in the 1955–7 inquiry, 353, or 41%, had avoidable factors, of which most were the responsibility of individuals, and only a small proportion due to administrative failures. One hundred of these deaths were due to ectopic pregnancy and abortion. There remained, therefore, 253 other deaths due to pregnancy and childbirth in which there were avoidable factors, and a further 57 fatal cases associated with pregnancy and childbirth which were thought to have avoidable factors. In 55 of these cases the patient herself was considered to be wholly responsible and in 26 partially responsible for the avoidable factor. Avoidance of avoidable factors in the hospital services might have saved 75 lives and assisted in saving eight more where the patient herself also contributed. Similarly, avoidance of avoidable factors in the domiciliary services might have saved 121 lives and helped in saving 18 others where the patient herself was also responsible. Thirty-three other lives might have been saved by better care from both the domiciliary and hospital services. It therefore appeared that during these three years two deaths occurred each week which might have been prevented. At least one in six of these errors was made by the patient herself.

The avoidable factors occurred in 197 deaths during the antenatal period, in 35 deaths during both the antenatal period and labour, in 63 during labour, in nine during the puerperium, and in four during both the antenatal period and puerperium. The basic avoidable factors during the antenatal period were very similar in the hospital and domiciliary services. The large majority were considered to have had inadequate antenatal care. In the group dying during labour, poor management was the primary avoidable factor. In hospital, junior medical staff sometimes attempted difficult operative deliveries unsupervised by their more senior colleagues. In the domiciliary service complicated malpresentation and difficult forceps deliveries were attempted under most unsuitable conditions. Failure to recognize the seriousness of the patient's condition resulted in delay in blood transfusion or in summoning the flying squad. In the puerperium lack of appreciation of the gravity of the patient's condition and, in hospital, the undertaking of surgical procedures which could well have been postponed were the chief faults.

Prevention of Maternal Deaths

Better and more intelligent antenatal care, with a proper selection of patients for hospital confinement, could prevent a substantial number of maternal deaths. For this purpose a well worked-out programme of antenatal examinations to cover the whole of normal pregnancy which was sufficiently flexible to allow more frequent supervision was essential. The results of such examinations must be assessed both individually and in relation to previous examinations. Where the care was undertaken by several individuals then each must be aware of the findings of the other. It was the lack of co-operation between such persons with no one clearly responsible which often resulted in a patient receiving poor antenatal care despite a quite adequate number of examinations.

The patient herself played a very important part in her own care, and the success or failure of the maternity service would ultimately depend on her. More investigation was needed into the reasons why women concealed pregnancy from doctors and midwives, and why they would refuse treatment to such an extent as to become the primary cause of their death. Better health education, more understanding of their problems, perhaps more considerate treatment in some hospitals, and more use of the home help service could be some of the ways in which the maternity services could help to save the lives of these unfortunate women.

Much, too, could be expected by the steady improvement in co-ordination of the three sectors of the maternity services. If the pace had been slow, the final result might be the more effective for that reason. If, therefore, the profession was prepared to study lessons that could be learned from these reports and to implement suggestions made in them, it was most probable, if not certain, that a maternal mortality certainly of two, and probably of one, per 10,000 births was obtainable. There were ample grounds for belief that childbirth would continue to become ever more safe and that no small part could be played by an unremitting vigilance on a national scale.

Ealing Borough Council is offering special encouragement to those traders who achieve a higher standard of hygiene than the law demands. It will issue a certificate to all food traders in the Borough whose premises and staff fulfil these special requirements. An outline of the requirements is that (1) The premises must conform to a high standard of hygiene. (2) Satisfactory control over pests must be exercised at all times. (3) The staff must have attended food hygiene lectures. (4) All new entrants will be required to have a radiograph of the chest at a mass *x*-ray unit. The certificate is renewable yearly, and will be withdrawn if the holder has failed to meet the requirements.

BRITISH ACADEMY OF FORENSIC SCIENCES

FIRST SCIENTIFIC AND GENERAL MEETING

The first scientific and general meeting of the British Academy of Forensic Sciences was held at the London Hospital Medical College on July 22 and 23. It was attended by some 58 members and their guests, and was devoted to a series of papers on the present position of the forensic sciences in Britain.

Education and Training

In his presidential address, Professor LEON RADZINOWICZ, Wolfson professor of criminology at Cambridge, emphasized that criminology could never be self-contained and that any advance in research into the causes of crime must be achieved through advances in the fields of medicine, psychology, psychiatry, and social science. Forensic medicine, forensic psychology, and forensic psychiatry should each be regarded as a separate discipline in its own right, and, while intercommunicating with police science, should otherwise be independent. It would be one of the major objects of the British Academy of Forensic Sciences to make enlightened public opinion aware of the underdeveloped nature of the forensic sciences in this country.

Dr. C. H. JOHNSON, secretary of the Police Surgeons' Association, underlined the urgent need for both graduates and undergraduates in Britain to receive training in forensic medicine. Undergraduates received little instruction in the subject at all. Attendance at the lectures was not obligatory, and often the examination papers contained no questions on the subject at all. In such lectures as were given there would be no more than a passing reference to the problems of homicide, suicide, and commercial and industrial injuries. No wonder the average practitioner shunned appearances in court and regarded them as a waste of time.

The police surgeon to-day was retained as the medical adviser to the chief constable in relation to cases which occurred in police work, and not, as was the case before the N.H.S., as the medical adviser to the members of the Force. While there were 127 police surgeons in the metropolitan area and similar appointments in other large cities, not every police station had its own police surgeon, and in rural districts the system still prevailed of employing all and sundry as police surgeons. The training of a police surgeon to-day was still based on the trial-and-error method of learning by experience. A diploma in forensic medicine for police surgeons was badly needed, and until it was provided the police surgeon would continue to be regarded as a biased witness and sub-standard doctor.

Dr. R. I. MILNE drew attention to the need for the coroner, who might have only had a vaguely scientific training, to be able to call upon competent experts to advise him. In the Trist case,* for instance, opinions by persons who were going outside their field of expert knowledge had led the Portuguese authorities to come to the erroneous conclusion that death had been due to food poisoning. He emphasized the need for the student to be taught not only how to give evidence but also to appreciate fully the nature and quality of the death certificate.

Toxicological Investigation and Research

Dr. F. G. TRYHORN reviewed the growth of the Home Office Forensic Science laboratories. The laboratories, of which there were eight serving England and Wales, had three main fields of investigation, (i) biology, (ii) chemistry, and (iii) physical methods. Within this range came the analysis, identification, and assay of any material in cases of homicide, suicide, and accident. Further, in motoring offences there was also the analysis of blood and urine for their content of alcohol, a class of work which might increase considerably if suggested legislation was enacted. On the biological side the examination of bloodstains formed an important part of the work. In these cases there were three questions to be answered: (*a*) Was the material blood? (*b*) From what species had it come? (*c*) From whom had it come? The laboratories could answer the first two questions completely. In the case of the third question the only conclusive answer that could be given was a negative one, since only the ABO system of grouping was used in evidence. There was a pressing need, therefore, in this field of research to extend the categories of grouping, particularly in cases of dried blood. "Physical methods" investigations included problems arising from accidents, burglaries, forgeries, and counterfeiting, the linking of bullets with cartridge cases, and the relation of marks, scratches, indentations, cuts, wounds, and impressions to the instruments that had made them. The present system could be improved by the provision of a central laboratory where the pressure of day-to-day work would be less and so allow more time for the training of laboratory staff.

Dr. F. C. IRVING SUNSHINE, dealing with facilities for toxicology in the U.S.A., received an envious hearing when he admitted that in the United States the toxicologist rarely lacked either instruments or floor space for his work. But the training of the toxicologist in the U.S.A. resembled that in the United Kingdom in the lack of organized courses. Of the present problems Dr. Sunshine singled out for special mention the difficulty of tracing drugs in the tranquillizer group, where between 1954 and 1959 no fewer than 19 new products came on the market. In most cases the drug companies had failed to provide any analytical data.

The Mortuary Situation

Dr. H. A. SISSONS, secretary of the committee appointed by the Association of Clinical Pathologists to investigate mortuary conditions, discussed the facilities for post-mortem examination. Most of our public mortuaries were historical relics, he said, and there was an enormous contrast between what was needed and what at present existed. This was true of both public and hospital mortuaries, and unfortunately the teaching hospitals gave no proper lead in reforming the present state of affairs. For an effective necropsy there must be an effective post-mortem room. In teaching hospitals it was surprising how much teaching of both students and nurses took place in inadequate post-mortem rooms. Staff and students returned direct to the wards and elementary considerations of bacteriological infection seemed to have been forgotten.

Basic standards must be laid down for such matters as refrigerated storage space, working area, and ventilation. Waiting-rooms for relatives and undertakers should be provided, together with a viewing-room and rooms for the pathologists. In teaching hospitals those carrying out the necropsy and those viewing it should be separated to eliminate the need for the students to tramp through the operating part of the room. This might best be achieved by means of a glass panel, and in any event there should be a separate area for the secretarial staff. Mortuary staff was generally of the porter class. Much should be done to improve their standing, which should be equivalent to that of laboratory technicians. They should be made financially independent of the present reliance on the "perks" of office and similar payments, which often came out of the pocket of the pathologist. Finally, the present law should be reconsidered with a view to giving coroners greater control over mortuary accommodation.

The criticism of the present mortuary situation was further developed by Dr. DONALD TEARE in a paper on "Facilities for Forensic Pathological Investigations," in the course of which he said:

"The mortuaries are the responsibility of the local authorities. Such are the petty jealousies of local government that, while some authorities will unite together to erect a suitable and economic

*See *Brit. med. J.*, April 11, 1959, p. 979.

mortuary for their joint areas, others will try not only to keep up with but to outdo 'The Joneses,' and each erects a mortuary as a living memorial to the chairman of the Public Health Committee. Small authorities sometimes spend tens of thousands of pounds on mortuaries to take a small number of bodies.

"Numerous small mortuaries make a great deal of travelling for pathologists. . . . While it may inconvenience relatives in that they have to travel a deal further to a combined mortuary, one trusts that they will only have to do so once in a lifetime, whereas the pathologist must make the journey two or three times a week."

Similar criticisms of the position were made by Dr. MILNE and Dr. GAVIN THURSTON, both metropolitan coroners, the latter referring specifically to the appalling state of the mortuaries in the London area.

Forensic Psychiatry

Dr. DESMOND CURRAN, speaking on forensic psychiatry, referred to the poor reputation of psychiatric evidence in courts of law in this country, that given by prison medical officers possibly excepted. Ordinary doctors got no instruction in forensic psychiatric problems, and the ordinary psychiatrist little more. Conversely the prison medical officer received little instruction in ordinary psychological medicine. Further, ordinary psychiatrists had very little experience of "normal" criminals, whilst the prison medical officer had very little experience of "normal" psychiatric cases.

The vast majority of prisoners were not psychiatrically abnormal (unless the term abnormal was used in a very special sense). The psychiatric aspect of crime was obscured by the confusion surrounding what was "normal." The problem was to distinguish the sick from the sinful, and this was "a sea with no shore." But more important than academic discussion on whether this or that condition—e.g., homosexuality—was a disease was the practical question: "What is the best way of dealing with the situation?" About 1% of those sent to prisons or Borstals were certified as insane or mentally defective, and according to experienced prison medical officers an additional 5–10% could be regarded as medical cases. In addition there were an indefinite number in whose treatment doctors could help.

One of the main difficulties was that, with few exceptions, psychiatrists, like other medical men, disliked giving evidence in court. The amount of time and disruption entailed both to the doctor and his patient was distressing, and there was inevitably a feeling that a court of law was not the best procedure for determining mental illness and the treatment most suited to the prisoner. Finally, the defence only presented the evidence which suited it, and solicitors could and did importune psychiatrists until they found one who was able to give the kind they wanted. Furthermore, it could and did happen that a psychiatrist might be put in the box and examined only on those aspects of the case which were favourable to the one side. Unless the other aspects of the report were brought out in cross-examination, the court might have less than half the relevant evidence before it. Finally, Dr. Curran posed the problem of professional privilege. If an examining psychiatrist told a prisoner that anything he said might come out in court, the obtaining of a full history was seriously prejudiced. If he did not warn the prisoner, where did he stand if he was cross-examined?

Shortage of Expert Scientific Witnesses

Mr. E. J. T. MATTHEWS, under-secretary to the Law Society, discussing the facilities available to accused persons in civil actions, stressed the urgent need for scientific witnesses who were ready and willing to give evidence in courts of law. Guilt or innocence often depended upon the evidence of experts qualified in highly technical fields of science. The facts they adduced and the views they formed upon those facts could not be tested without the help of another specialist in the same field. In the speaker's opinion the scales were tilted in favour of the prosecution in this respect. Even where the defence succeeded in obtaining the services of a suitably qualified expert there were still obstacles to be overcome. There was no provision under the Criminal Legal Aid Scheme whereby the expert's fee could be authorized by the court in advance, and if the solicitor agreed a fee with the expert his own pocket might be at risk. In some districts it was difficult for the defence to obtain details of reports—e.g., post-mortem examinations—carried out for the prosecution. Not all pathologists were infallible, and it was wrong that the defence should be put to difficulty in testing the inferences drawn by prosecution experts.

In civil actions medical evidence was needed primarily in connexion with two classes of cases: matrimonial causes, particularly those relying on cruelty, where it was necessary for the petitioner to show that the respondent's conduct had affected her health; and personal injury cases, particularly traffic and industrial accidents. In the former case, while general practitioners appeared to be willing to certify injury to health with abandon, they showed some reluctance to testify to that effect in court. Happily for the parties in the action, the service of a subpoena was usually effective. With the latter, the evidence required by the court usually comprised a description of the injuries, a history of the treatment and recovery, and a prognosis. The doctor best qualified to give that evidence was often the consultant who had treated the patient. But consultants were often unwilling to give such evidence and refused, either by quoting a prohibitive fee or by insisting on an undertaking that they would not be called to give evidence in court. Mr. Matthews questioned whether a doctor should withhold the value of his medical skill when it was needed in connexion with legal proceedings, in view of the fact that doctors were responsible for the rehabilitation of those whom they accepted into their care.

Other papers in this session on "Evidence and Witnesses" were read by Mr. L. C. NICKOLLS ("The Scientist in Court") and Mr. F. LAWTON, Q.C. ("The Rules of Evidence, the Keeping of Scientific Records, and the Admissibility of Statements").

At the Annual General Meeting Professor RADZINOWICZ was elected president of the Academy, Dr. FRANCIS CAMPS was elected secretary. The annual general meeting will be held at Cambridge.

MR. ENOCH POWELL MINISTER OF HEALTH

The Prime Minister has chosen Mr. ENOCH POWELL to succeed Mr. DEREK WALKER-SMITH as Minister of Health. This was announced from 10, Downing Street late on Wednesday, July 27. Mr. Powell, 48, was formerly Financial Secretary to the Treasury, but resigned with the then Chancellor of the Exchequer, Mr. Peter Thorneycroft, in January, 1958, because of disagreements over financial policy. Mr. Walker-Smith, who has been Minister of Health for three years, is made a baronet.

Professor at 25; Brigadier at 32

Mr. J. Enoch Powell was born in Stechford, Birmingham, in 1912. From King's Norton Secondary School he won scholarships to King Edward's High School and thence to Trinity College, Cambridge, where he was a Craven scholar, first Chancellor's classical medallist, Porson prizeman, and Browne medallist. He took an honours degree in 1933. Subsequently he studied and travelled in Italy as a Craven travelling student, returning to Trinity College as a Fellow in 1934. In 1937 he was appointed Professor of Greek in the University of Sydney, New South Wales—an appointment he held until the outbreak of the second world war.

Mr. Powell returned to the United Kingdom in 1939 and enlisted in the ranks of the Royal Warwickshire

Regiment. He was commissioned in 1940, and subsequently served on the General Staff in the Middle East, North Africa, South-East Asia, and India. He was awarded the M.B.E. in 1943, and attained the rank of brigadier the following year. After demobilization he joined the Conservative Parliamentary Secretariat and was joint head of the Home Affairs Section of the Conservative Research Department until 1949.

In the 1950 General Election Mr. Powell won Wolverhampton, South-west, from Labour with a majority of 691 votes in a three-cornered contest. In October, 1951, his majority rose to 3,196 in a straight fight, and in the May, 1955, General Election it rose to 8,420 after a substantial redistribution. He was chairman of the Party's Parliamentary Committee on Housing, Local Government, and Works from 1954 to 1955, director of the London Municipal Society, 1952–5, and chairman of the Party's

National Advisory Committee on Political Education, 1953–5. In November, 1955, he was elected vice-chairman of the "1922 Committee" in the House of Commons. In December, 1955, he was appointed Parliamentary Secretary to the Ministry of Housing and Local Government, and in January, 1957, he became Financial Secretary to the Treasury. He resigned from this appointment in January, 1958. At the last General Election Mr. Powell was returned with a majority of 11,167 in a straight fight, and in the following month he was elected chairman of the Conservative Party's Parliamentary Finance Committee and a member of the Executive of the 1922 Committee.

Mr. Powell has published several books on classical and other subjects, including four books of poems. His classical writings have been principally on Herodotus. He is one of the authors of *One Nation—A Tory Approach to Social Problems*, published in 1950, and joint editor of *Change is Our Ally*, published in 1954. In 1952 he published *The Social Services: Needs and Means* in collaboration with Mr. Iain Macleod, M.P. In 1955 he published *Biography of a Nation* in collaboration with Mr. Angus Maude, M.P.

In January, 1952, Mr. Powell married Miss Pamela Wilson, who was his colleague in the Conservative Research Department. They have two daughters.

Nova et Vetera

AN EDINBURGH CENTENARY

This volume* celebrates the birth of the Royal Edinburgh Hospital for Sick Children in 1860, and it has a distinguished story to tell. Many children's hospitals the world over have already celebrated, or are approaching, their centenaries. Great Ormond Street Hospital is now 108 years old and the Philadelphia Children's Hospital is 105 years old. Several European hospitals are much older than these, the oldest being L'Hôpital des Enfants Malades in Paris which was founded in 1802.

Medical readers will be interested in the record of great physicians and surgeons who have contributed to the fame of this splendid Edinburgh institution. The most famous of them all, John Thomson, was a true pioneer and gave his whole life to the study of disease in childhood. He and his English colleagues, Barlow and Still, dominated paediatrics long years before this magic word was discovered by the inventive Americans. Charles McNeil, happily still with us, was in direct apostolic succession, and he became the first professor of child life and health in the University of Edinburgh in 1931. Two brilliant surgeons, Sir Harold Stiles and Sir John Fraser, did their best work in this hospital.

The book contains some curious facts which may be new to some readers, as they were to me—as, for example, that diseases of children were in the nineteenth century linked with obstetrics and gynaecology. Thus, one of the original physicians on the staff was Matthews Duncan, who later became obstetrician to St. Bartholomew's Hospital and delivered the Royal ladies (did he indeed hold a chair of midwifery at Bart's ?).

Professor R. W. B. Ellis, in a final chapter, shows that the hospital is adapting itself with foresight and flexibility to the changing requirements of to-day and to-morrow. Dr. Guthrie, with the help of eight contributors, has edited an admirable history. The book is well produced and amply illustrated.

D. V. HUBBLE.

DUCKING MAKES A DOCTOR

These are the entertaining family recollections of a distinguished lawyer who as a small boy from his nursery window surveyed the elegant parties in the grounds of Montagu House, sunny occasions when the *élite* were regaled by the band of the Guards.† On Sunday afternoons in winter he gazed beyond the bath-chair stand in George Street in search of his friend the muffin man. Miss Woodman's Academy, which he attended, is now part of Selfridges; the halfpenny horse bus which later took him to Dean's Yard trundles no more, and gone are the boxes at Pamphilons ("We have cabinet pudding on to-night, Sir"). Gone, too—though some will remember it—is the Roebuck Inn in "the Corn" where he was taken by his father for a bottle of Bollinger to celebrate his acceptance at Magdalen.

Sir Harold was called to the Bar in 1899 and took silk in 1921. His father, Malcolm Alexander Morris, fell into a dock at the age of 15 and was so well treated at the Bristol Royal Infirmary that he determined to become a doctor. One of his first patients was a groaning tramp in a hayloft who turned out to be moribund with smallpox. At Goole he was hissed at the funeral of his first unsuccessful case, so he was glad to return to London, where he set up as a dermatologist and was saved from penury by a hirsute girl who attended for weekly epilation. In due course he

**The Royal Edinburgh Hospital for Sick Children, 1860–1960.* By Douglas Guthrie, with various contributors. (Pp. 75+xii; illustrated. 17s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

†*Back View.* By Sir Harold Morris, Q.C. (Pp. 244; illustrated. 25s.) London: Peter Davis. 1960.

removed a blemish from the face of his monarch and was rewarded with a K.C.V.O. and fame. Then came many a golden sovereign and shilling piece discreetly left in screws of paper on the mantelpiece by satisfied patients. There are anecdotes of West End doctors, including Sir Anderson Critchett, who thoughtfully provided sherry and sandwiches at 11.30 for all in his waiting-room, and Conan Doyle, who, on the advice of Dr. Morris, housed Sherlock Holmes at 21, Baker Street, formerly the home of the Morris family. (The number 221B was chosen only to mask identity.) Let us remember that Holmes dispatched his telegrams from the Wigmore Street Post Office and Watson bought tobacco at Bradleys in Oxford Street.

Great-grandfather offers guidance to his teenage daughters for their conduct on a voyage to Madras in 1821. Prayers, playing on the harp, and uplifting reading were to occupy their mornings, with port and biscuits to be partaken in their cabin at noon: plain fare and edifying conversation at the dinner table and then back to their cabin for the singing of psalms. No backgammon or pineapples, please; no trips ashore, and not too long at the cuddy. They were to hang nothing out of the porthole. Exercise was virtually impossible, for in the morning the deck would be wet, during the day the sun would be too hot, and at night the young men would be in no fit state for the chaste company of damsels. Moreover, the supporting arm of some gentleman would be necessary, so one of them (—dear Georgiana, I am sure it would *always* have to be you ! —) would remain in the cabin while Susannah and Rosanna would chaperon each other on this exciting adventure. Perhaps their lives were not so sheltered as Papa had imagined, for within a year or so these three innocent maidens had married.

W. H. MCMENEMEY.

ALEXANDER GORDON

A SCOTTISH FORERUNNER OF SEMMELWEIS

Alexander Gordon, of Aberdeen,* has certainly been one of the neglected pioneers of British medicine, but, true as this statement is, it cannot be accepted without reservations. He was a pioneer in so far as he demonstrated and published his proof, based on his own careful scientific records, that puerperal fever was contagious and that it was carried from one obstetrical case to another by the doctor and the midwife. This discovery influenced the practice and teaching of some of his distinguished contemporaries and immediate successors (such as Denman and Hey), was cited admiringly by Oliver Wendell Holmes in his own classic paper on the subject in 1843, and has been duly recognized by Lea, Thoms, Colebrook, and a few others. If this does not indicate neglect, neither does it indicate universal recognition of an undisputed claim. It is unfortunately true that we are slow to accept new ideas, and that often the same truth has to be given to the world several times over before it is seen for what it is. The time and the place are factors as important as the man, and it is these which were wrong for Gordon.

He was born in Aberdeenshire in 1752 and died there in 1799, having spent only ten years of his short life away from his native land, during which time he served as a naval surgeon and received specialist training in obstetrics in London. It was a period when the importance of cleanliness was not generally appreciated. The reaction of Gordon's colleagues to his treatise of 1795 was no different from that provoked by Semmelweis in Vienna 50 years later. Gordon had to abandon his hitherto flourishing practice and return to naval service, where he contracted the tuberculosis from which he died four years later. Had he lived the normal span he would probably have returned to the charge and won wider recognition for his views. Why, then, is Semmelweis a popular hero and Gordon's name unknown outside specialist circles ? Semmelweis proclaimed his views in a renowned medical centre, Vienna, at a time when the great age of German pathology was dawning and when his younger contemporaries, some of them the founders of modern bacteriology and epidemiology, and already familiar with an episode which had a local notoriety, were able to show the world how right he was.

In bringing Alexander Gordon to our notice, Dr. Ian Porter must not expect to see Semmelweis toppled from his pedestal. The first apprehension of truth is an important stage in enlightenment, but the advance is not accomplished until the truth is established as a commonplace. Dr. Porter's book is the most comprehensive account of Gordon's life and work yet written and deserves to succeed in its purpose of restoring to Gordon his just place in the history of obstetrics, which is alongside White, Holmes, and Semmelweis.

F. N. L. POYNTER.

**Alexander Gordon, M.D., of Aberdeen, 1752–1799.* By Ian A. Porter, M.B., Ch.B. (Pp. xii+92; illustrated. 12s. 6d.) Aberdeen University Studies Number 139. Edinburgh and London: Oliver and Boyd for the University of Aberdeen. 1958.

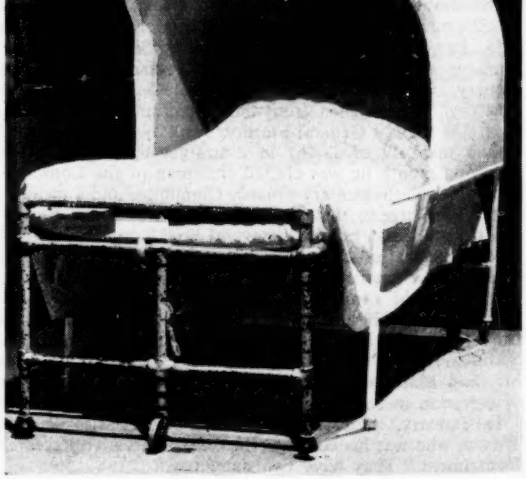
New Appliances

NOISE-REDUCING HOOD

Mr. B. N. CATCHPOLE, University Department of Surgery, Royal Infirmary, Sheffield, writes: It is not always possible to isolate a noisy patient in hospital, nor is it always easy to protect from surrounding noise a patient needing quietness. It was thought, therefore, that a portable sound-proofed hood, similar to those of certain open-type telephone booths, placed over the head of such a patient's bed might prove useful.

When tests were made by means of a whistle blown by compressed gas under a prototype hood with a microphone and cathode-ray oscillograph recording sound waves, it was found that 10 yards from the side of the hood the apparatus reduced wave amplitude to one-quarter and to one-half directly facing its open end and five yards away.

The final hood is shown in the illustration. It consists of a framework of copper tube covered by hardboard. The inside is lined completely with plastic foam (1½ in. (3.8 cm.) thickness), which not only acts as an efficient sound-insulator but also cushions any wild movement of the patient. A low-power protected light is fitted in the top of the hood to



permit observation of the patient. The whole apparatus is made to fit a standard hospital bed with side rails in place. Two wheels enable it to be moved readily, and it is light enough to be handled by one nurse. When the hood is in position the bed can be pulled forward to permit nursing care of the patient if this is not possible otherwise.

The bulk of the hood is certainly a drawback, but a modified design might overcome this objection. The illustrated apparatus was built in the workshops of the Sheffield Royal Infirmary for approximately £20, exclusive of labour. My thanks are due to the hospital staff for their care in its construction, and particularly to Professor A. W. Kay for his encouragement, and the Medical Board of the Royal Infirmary for defraying the costs involved.

MANIKIN FOR TRAINING IN EXPIRED-AIR RESUSCITATION

Dr. HENNING RUBEN, Director of the Department of Anaesthesia, the Finsen Institute, Copenhagen, writes: It is generally agreed that manual methods of artificial respiration are not always effective, particularly because of their failure to open the air passages. In many countries, therefore, these methods are being supplemented or substituted by one which, based on mouth-to-mouth insufflation, is more likely to produce the necessary respiratory exchange.

The person-to-person method has serious objections. Even if the possibility of transmitting serious infection is a reasonable risk in an actual emergency, it is not justifiable during training. Also, one could not really tell whether the method was being performed properly, as the "victim" is unable to relax the pharyngeal structures sufficiently.

To overcome these difficulties in training, a special teaching-aid, a manikin, has been developed, based on two years' experience in teaching expired-air methods.

The manikin (Fig. 1) consists of a head, a neck, and a torso. Two bags on the torso, constituting the lungs and the stomach of the manikin, are in tubular connexion with its nose and mouth. The neck can be flexed or extended, and its jaws can mimic normal mouth movements and be pushed or pulled forward.

The mode of action is as follows (Figs. 2 and 3). When the manikin is in a resting position the neck is slightly flexed, thereby maintaining total obstruction of the air passages. When inflation is tried, therefore, no air enters the lung or the stomach. By tilting the head backward, or by manipulating the jaw, the air passage to the lungs is opened, but only if done the correct way. If the jaw is pulled or pushed forward, and the head is not tilted back, the air passage will not open and there will still be total block. Also, extension of the head maximally without jaw manipulation will open the airway, in accordance with methods used in expired-air resuscitation. When blowing through the nose of the manikin, its mouth must be closed, as otherwise air will leak through it. If, with the air passage of the manikin fully open, too much force is used during blowing, its stomach will inflate in addition to its lung. Where, therefore, the manikin's air passage is adequately opened and the correct blowing-force is used, then its lung, and the lung only, will be inflated.

Finally, bronchial spasm can be imitated on the manikin. Because resistance to inflation of air is stronger through the nose than through the mouth, air blown with a certain force will be less apt to inflate the stomach when blown through the former. Exhalation of air from the lung occurs quickly and quietly, provided the air passage is kept open. The air in its stomach empties only very slowly unless pressure is exerted on it, say, by hand. The two bags on the torso produce lifelike movements of its chest and abdomen, so that the trainee can see that the chest movements are correct and recognize when gastric inflation occurs. From this action of the manikin the instructor can check the performance of the trainee—especially

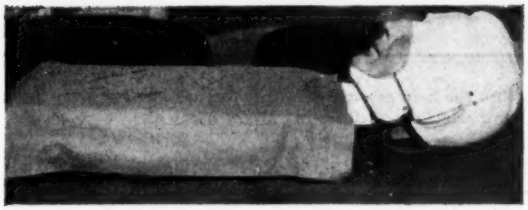


FIG. 1

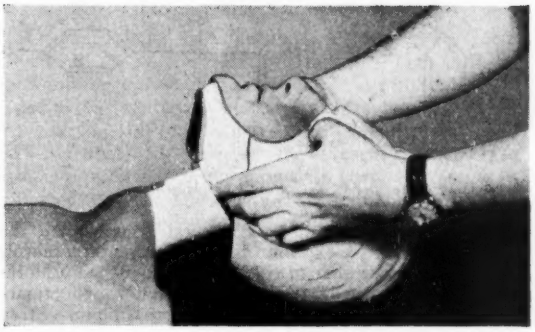


FIG. 2

FIG. 3

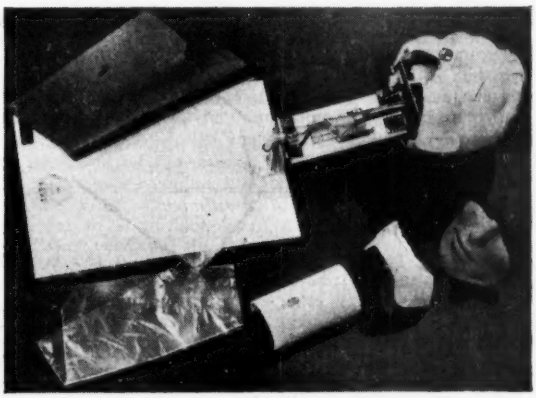


FIG. 4

distinguishing between failure to open the air passages and to obtain a non-airtight seal, and blowing with the proper force.

The manikin, which imitates the unconscious apnoeic victim in important respects, makes practical training in

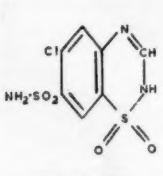
(*Continued at foot of next page*)

To-day's Drugs

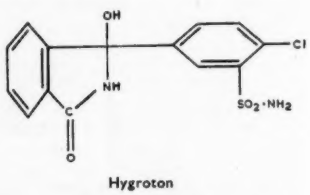
With the help of expert contributors we publish below notes on a selection of drugs in current use.

"Hygroton" (Geigy).

Chemistry. — This is 1-oxo-3-(3'-sulphamyl-4'-chlorophenyl)-3-hydroxy-iso-indoline. As the following structural formulae show, it has a relationship with chlorothiazide:



Chlorothiazide



Hygroton

Pharmacology.—Hygroton is an oral diuretic, and the pattern of electrolyte excretion in the urine suggests that its action is similar to that of chlorothiazide and hydrochlorothiazide. To judge by bicarbonate excretion and urinary *p*H, hygroton has little carbonic anhydrase inhibitory effect. A dose of 400 mg. induces a diuresis in about two hours, and there is approximately equimolar elimination of sodium and chloride ions, though sometimes there is a slightly greater excretion of chloride than sodium. As with the thiazide compounds, excretion of potassium is increased, and this is attributable to Na and K exchange in the distal renal tubule. The action of hygroton is often prolonged and may last 24–48 hours. In part this effect may be due to the low solubility of the drug, which is only slowly absorbed from the gastrointestinal tract.

Therapy.—Hygroton may be given for the symptomatic relief of oedema caused by cardiac, renal, or hepatic disease, and will also potentiate the antihypertensive action of ganglionic-blocking drugs and others that lower blood-pressure. Each tablet contains 100 mg., and a single dose may range from 100 to 400 mg., depending on the severity of the patient's oedema. Treatment of oedema should be intermittent and given on two or three days each week.

At the present time there is insufficient evidence to know whether hygroton has any advantage over the longer-established thiazide diuretics in clinical practice.

Side-effects.—No toxic effects have yet been reported, but hygroton may induce depletion of potassium, with a liability to coma in hepatic cirrhosis and intolerance to digitalis in cardiac failure. When treatment is prolonged and the patient's intake of potassium is low, supplements of potassium chloride must be given.

N.H.S. Basic Price.—100 tabs., 71s. 5½d.

(*Continued from previous page*)

resuscitative procedures a second nature to the layman rescuer. Also, it can be used for training in bag-and-mask ventilation, as well as other expired-air methods.

The head of the manikin can be taken to pieces like the other parts (Fig. 4). All the valves acting on the air passages are placed outside the air passages. The nose and mouth, with adjacent parts of the face, join into a single piece. They can be sterilized, say, while a spare mouth-and-nose piece is being used. Furthermore, the lung and stomach bags and the tubing which leads from the mouth–nose piece can be flushed with sterilizing solutions, or exchanged with another tubing after use—safe precautions against cross-contamination of the trainee.

The manikin is manufactured by Test Laboratorium, 22, Kastanie Alle, Copenhagen.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

New Rashes for Old

SIR,—During the past month we have encountered in practice an outbreak of febrile illness in children, of which the presenting features were rash, adenitis, headache, and vomiting. The oldest child seen was aged 10 years and the youngest was 10 months.

The rash presented in two forms, both of which might be present concurrently: a blotchy, bright pink, maculopapular eruption was common on the face, while on the trunk and limbs the rash was usually composed of tiny, discrete papules which were often colourless and seen only by reflected light. This form of the rash was frequently described by the mother as "under the skin." Rashes sometimes lasted only a few hours, but more commonly persisted for 3–4 days.

Most of the patients recovered rapidly and without complications, although one boy of 8 years was admitted to hospital with aseptic meningitis some two weeks after the onset of his initial illness, from which he had apparently recovered. This is of interest in view of the fact that there has been an increased number of admissions of aseptic meningitis to the infectious diseases hospitals in the city during this same period. Rash was a feature in only a small number of these.

Thirteen families were visited to obtain specimens of stool or rectal swabs, and throat swabs, from patients and their contacts. Investigation revealed the presence of E.C.H.O. virus type 9 in six of the families; from a further four families virus has been isolated and is awaiting identification. E.C.H.O. virus type 9 has also been isolated from several cases of aseptic meningitis admitted to Ruchill Hospital. Although evidence has been obtained of infection with E.C.H.O. Type 9 virus in previous years, we are unaware of any outbreak in Glasgow as striking as the present one.

Inquiry of our practitioner colleagues has shown that illness of this type has been recognized in other areas of the city. The interest in E.C.H.O. virus infections shown in your columns in recent weeks has encouraged us to report the outbreak; perhaps others who are seeing similar cases will also report their experience of "New rashes for old."—We are, etc.,

JOAN B. LANDSMAN.
H. MACANESPIE.
W. J. WEETCH.
ELEANOR J. BELL.

University Department of Infectious Diseases and the Virus Laboratory, Ruchill Hospital, Glasgow, N.W.

Storage of Red Cells for Blood-grouping

SIR,—Drs. R. G. Huntsman, B. A. L. Hurn, and H. Lehmann (July 9, p. 118) describe a technique for the storage of red cells for blood-grouping by freezing in liquid nitrogen. The procedure offers certain difficulties, such as the need to store at the very low temperature of carbon-dioxide snow and the necessity to replenish the nitrogen from time to time when storing larger volumes of blood. The authors offer the method as an alternative to storage in glycerol,[1] the latter requiring care and patience in the tedious recovery process.

In 1958, Macdonald and Marsh[2] described a modified recovery technique for cells stored in glycerol which

resulted in a considerable saving of time compared with the method of Chaplin and Mollison[1] and which caused less haemolysis during recovery than Lovelock's technique.[3] It was found that by increasing the citrate concentration, the number of glycerol dilutions can be decreased. The technique, which is described below, has been in use in this blood transfusion centre for three years.

The cells are removed from the refrigerator (−20° C.) and allowed to thaw at room temperature. As soon as the cells are thawed the tube is filled with solution 1 (approximately four times the volume of the cell/glycerol mixture). The contents of the tube are mixed and then centrifuged at 1,500 r.p.m. for four minutes. Discard the supernatant fluid and replace with solution 2. Re-suspend the cells and centrifuge. Replace the supernatant fluid with solution 2 diluted with an equal volume of 0.85% saline and again mix and centrifuge. The cells are then washed once in warm 0.85% saline (37° C.) and are ready for use. (*Solution 1:* 12% glycerol in 5% trisodium citrate. *Solution 2:* 5% glycerol in 5% trisodium citrate.)

—We are, etc.,

W. J. JENKINS.
W. L. MARSH.

North-east Metropolitan Regional Blood Transfusion Centre, Brentwood.

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Bell's Palsy

SIR,—Dr. J. A. Gordon's account (July 2, p. 72) of two cases of spontaneous facial paralysis occurring in the same house ends my search of the literature for a like experience to my own, which occurred in August, 1958.

A boy of 7 years presented on August 15, 1958, with a left lower motor-neurone facial paralysis of twenty-four hours' duration, which had been preceded by a couple of days of general malaise. There was no evidence of any other lesion in the central nervous or other systems. He had been vaccinated against poliomyelitis some months previously. Four days later, his sister, then aged 4 years, developed an identical lesion. The boy took three weeks to recover completely and the girl nearly six.

A day later I saw the same lesion, on the same side, in a boy of 5 years who lived about half a mile from the other cases and who had no known contact with them. This boy had complete recovery in three weeks.

Inquiry locally and from the Medical Officer of Health brought no further cases to light, and virus studies showed no evidence of polio, Coxsackie, or E.C.H.O. virus infection, and there was no haematological evidence of mononucleosis. Serological studies for varicella antibodies were not done, but there was no chicken-pox or zoster in the district.

The causative agent of spontaneous facial paralysis is still quite unknown,[1] although the infective nature of the condition, which Dr. Gordon's and my cases tend to substantiate, is now widely believed in.[2 3] Of the known infective causes of facial paralysis, poliomyelitis is the most important clinically, as nearly a third of cases do not get full recovery.[4]

I feel that notification of all cases of facial paralysis in the younger age-groups is justified, so that virus studies could be done in the early stages.

I would like to thank Dr. B. P. Marmion, of the Public Health Laboratory Service, for undertaking virus studies and for helpful comment. Likewise Dr. D. B. Bradshaw, medical officer of health, Leeds, and Dr. D. Taverner, of the department of medicine, University of Leeds.

—I am, etc.,

Leeds, 8. M. DALES.

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Fat, Calcium, and Coronary Disease

SIR,—In a letter in your issue of May 28 (p. 1660) Dr. A. R. P. Walker refers to the very high milk-fat consumption in certain population groups in Somaliland and Eritrea—nomads who subsist throughout much of the year on the milk of goats, cows, and sheep—and asks whether, in view of the present tendency to associate milk-fat consumption with coronary disease, it is not desirable to investigate these people to see if they show much evidence of this disease amongst them.

Morris[1] has already shown that "the trend of consumption of butter-fat in the United Kingdom showed absolutely no relation; the steep increase in coronary deaths since 1943 was only one illustration of this." Nevertheless Walker's suggestion would appear sound, in procuring excellent further evidence on this subject, but has not the same thing been at least partly accomplished before? Half a century ago Metchnikoff, at that time a director of the Pasteur Institute, drew the attention of the medical profession throughout Europe to the longevity of certain groups of Bulgarian peasants, who lived largely on milk and milk products, including cheese. So striking was this longevity, in the opinion of observers at that time, that special studies were made of the bacteria in the cheeses they consumed, and the *Bacillus bulgaricus* was discovered. Metchnikoff announced his conclusions in his *Prolongation of Life*, the English translation of which, by Chalmers Mitchell, appeared in 1907. *120 Years of Life*, by Reinhardt, was on the same theme. To this day the consumption of cream cheese, yoghurt, and allied products is considered by some to be an excellent recipe for longevity.

There is no need to discuss at this point the supposed elimination of intestinal toxaemia on which these works were based—the only thing that need detain us here is at least the absence of early deaths in these high consumers of milk and milk products. Of that at any rate there would appear to be no reasonable doubt. As a matter of fact, the good opinion of milk and milk products is of great antiquity. For example, when Abraham entertained the three angels he set before them "butter and milk and a calf which had been dressed" (*Genesis*, Ch. 18, v. 8). And Moses in his fifth book sets forth the foods which Jehovah had given his people to eat. Amongst them was "Butter of kine, and goat's milk, and fat of lambs. . . ." (*Deut.*, Ch. 32, v. 14). What would this patriarch have thought of the new idea of substituting soya bean, sunflower seed, and other alien vegetable oils for the cream in milk, as a means of preventing coronary disease? Is it possible that he might have defended what was laid down to him by asking whether it was entirely fortuitous that, in a recent study where the above substitution was actually made, the consumers of the resulting product were the inmates of a lunatic asylum?[2] Would the ordinary man stand for it? And if it were argued—which, so far as I know, it is not—that substitutions of this type apply only to treatment, is it logical to make dietetic prevention different from dietetic treatment in this disease?

Arguing on a very different basis, I have myself tried to show[3–5] how, on evolutionary grounds, such unnatural substitutions can never hold the answer to

the problem of preventing coronary disease; and that great improvement in fat consumption can be achieved very simply, avoiding any conflict with evolutionary principles, by eliminating the excess fat at present being consumed through the sophistication in our food and in our eating habits.—I am, etc.,

Lee-on-Solent, Hants. T. L. CLEAVE.

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Just What the Doctor Ordered

SIR,—The General Practice Teaching Unit of Edinburgh University (July 23, p. 293) works under conditions that most family doctors must envy; each doctor appears to have a list of 1,200, with nursing, secretarial, and social worker help, and he averages about 22 consultations a day. Even allowing for teaching obligations, this should be general practice in the most favourable circumstances.

Figures of disease incidence do not necessarily give a satisfactory picture of what goes on, but only of the doctor's way of looking at it. For instance, the incidence of psychoneurosis is listed as 3.64% episodes of illness. But many more illnesses are emotionally determined. How many of the cases of dyspepsia, eczema, asthma, "vague symptoms," and even repeated coryza and superficial injuries are really bound up with undiscussed emotional conflict? In fact, one may ask in some cases, are these diseases or are they symptoms? It is clear from the content of the section on "Talking and Listening" that Dr. Richard Scott and his fellow-workers are aware of this. Yet in this practice with ample time and opportunity, discussion of personal relationships and therapeutic listening, the main tools of psychotherapy, took up only 6.6% of the consultations.

Does not this finding, in doctors so aware and so favourably placed, indicate that, as indeed they suggest, there is something wrong with the bias of medical education? Is there not needed in the medical schools not only more training in psychiatry, but an incorporation in the teaching of all branches of medicine of a due appreciation of the emotional background of disease?—I am, etc.,

London, E.11. SIDNEY ABRAHAMS.

Intestinal Obstruction after Splenectomy

SIR,—When a sudden increase or decrease in pressure occurs in a closed cavity—for example, the skull or thorax—it is liable to cause a displacement or shift of the contents of the cavity. A massive extradural haemorrhage produces generalized pressure symptoms on the brain and sometimes foraminal impaction. The removal of a lung causes displacement of the heart and mediastinum. In the abdomen the consequences of sudden alterations of pressure are not so pronounced, because the abdomen, not being a rigidly enclosed cavity, is more adaptable to pressure effects. In the abdomen, moreover, most of the intestine is but loosely attached posteriorly by the mesentery, and this allows a more gradual adaptation of the intestinal contents to changed pressure conditions. There are, however, parts of the intestine which are firmly anchored to the posterior abdominal wall with which loosely attached bowel is directly continuous. At the duodeno-jejunal flexure the fixed duodenum is directly continuous with the mobile jejunum. The removal of a greatly enlarged spleen creates a dead space which must be filled by mobile contents lying adjacent to it. The jejunum, by moving to the left, could be expected to cause kinking by traction on the flexure. In the case to be described it is believed that such kinking was produced with resultant obstruction.

An African boy, aged 12 years, was admitted with pain and swelling on the left side of the abdomen following a kick by a cow the previous day. He had vomited twice. Examination revealed restlessness, pallor, pulse 128, temperature 101° F. (38.3° C.). The spleen, which extended about five inches below the costal margin, was acutely tender. Shifting dullness was present.

On laparotomy, the spleen was found torn almost in half. One and three-quarter pints (1 litre) of blood were ladled out of the peritoneal cavity, mixed with potassium citrate, and given intravenously after the infusion of a pint of blood from a donor. The spleen was removed and the abdomen drained. The spleen weighed 3 lb. (1.4 g.). Next day the patient vomited three times, but the following morning, after intestinal movements had recommenced, an enema was given with the liberal expulsion of faeces and flatus. The patient, however, continued to vomit, and gastric suction was instituted. It was discontinued on the third post-operative day, though bile was still being withdrawn, upon which vomiting recommenced. On reinstituting gastric suction, quantities of bile-stained fluid up to 70 ml. continued to be withdrawn at hourly intervals. The presence of borborygmi on auscultation indicated an organic obstruction.

The abdomen was reopened on the fourth day, when the jejunum was found collapsed and normal peristalsis was present. The obstruction appeared to be at the duodeno-jejunal flexure or just proximal to it, where the superior mesenteric vessels anchor the duodenum firmly to the posterior abdominal wall. The release of pressure on the left side of the jejunum from the removal of the enlarged spleen had apparently produced dragging and kinking of the gut. In spite of gastric suction the stomach and duodenum were moderately dilated. A posterior gastro-jejunostomy was therefore performed. A duodeno-jejunostomy would perhaps have been theoretically correct, but would have taken longer, and the patient's general condition was unfavourable. After the second operation recovery was rapid and uneventful.

The point which I wish to stress is that this was an organic obstruction—not a paralytic ileus—which was, I think, directly due to the mechanism suggested above.—I am, etc.,

Lilongwe African Hospital, Nyasaland. S. V. HUMPHRIES.

Percutaneous Splenic Pulp Manometry

SIR,—I realize only too well how difficult it is to compress a subject into the limited space of an annotation, but I must protest about the apparent ignorance, inaccuracy, and bias of your annotator on the subject of percutaneous splenic pulp manometry (July 16, p. 206). Anyone unfamiliar with this topic is bound to gain the impression that this is a new technique, developed entirely (according to the references) in the United States. In fact intrasplenic pressure measurements in portal hypertension were made by Sherlock and her colleagues in 1954,[1] and transplenic portal venography was described as long ago as 1951.[2]

Use of the combined technique has also been reported from Dr. Sherlock's department,[3] and has been widely employed since. Nowadays any unit which undertakes the management of patients with portal hypertension carries out these methods of investigation as a routine. Finally, I am interested to note that according to you, Sir, there are 683 volumes of the *Annals of Surgery*. Do they all contain nearly 2,000 pages of text ?—I am, etc.,

Dudley Road Hospital, Birmingham, 18. A. PATON.

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*** The purpose of our annotation was to review some recent work in this field, not assign priorities. We apologize for the error in the reference, which should have read: Taylor F. W., *Ann. Surg.*, 1957, **146**, 683.—ED., *B.M.J.*

Accidental Arsenical Poisoning

SIR,—With reference to the case of accidental arsenical poisoning from acetarsol pessaries (July 16, p. 242), it was mentioned that a medical witness "had not been able to find any account in the literature of a similar case." The coroner's remarks "that from this single case it was now known that a treatment that was thought safe was potentially dangerous" were also quoted.

In the course of investigating deaths ascribed to encephalitis for the 12 months July, 1950, to June, 1951, I came across a similar death to which poisoning from arsenical pessaries "could not be excluded." A note to this effect appeared in the account of the investigation.[1] With two recorded deaths, added point is given to the coroner's remarks.—I am, etc.,

Croydon, Surrey. C. GRANT NICOL.

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Recording the Whoop

SIR,—The diagnosis of pertussis has always presented difficulties, which have been increased by the beneficent attenuation of the disease and the modification of the cough, produced by the prophylactic vaccines now in use. Quite recently, in my practice, the question arose in regard to twins, aged 7, as to whether the cough which one had developed was in fact pertussis. The usual expedients were tried, i.e., giving the child a crumbly biscuit, and chasing the child round the garden: the latter method certainly produced a cough which was by no means typical. The child's mother remarked: "I wish you could hear the cough when she is put to bed; it is quite different." It then occurred to me to ask whether they had a tape recorder, and I found that they could produce a very good one. We arranged for some recordings to be made at bedtime. A day or two later I heard the recordings and these, in my opinion, put the diagnosis of pertussis beyond doubt.

It is not my purpose to compete with the mysteries of the "black box," of which we have heard quite enough recently, for we cannot suppose that the diagnosis of scabies or ingrowing toenails would be made any easier by tape recording, but I seriously suggest that it might prove to be a very valuable means of confirming the diagnosis of pertussis, as there is little doubt that the cough tends to be very much more characteristic at night—a very convenient time for exploiting the method.—I am, etc.,

London, N.W.7. A. H. MORLEY.

Meigs's Syndrome

SIR,—I enjoyed Dr. E. Laidlaw Thomson's description (June 18, p. 1866) of a patient with right-sided pleural effusion due to an ovarian carcinoma as a case of Meigs's syndrome. This term should really be restricted to those cases due to an ovarian fibroma as defined by Meigs himself.[1] The looser use of the term could, however, serve a useful purpose if it were extended to cover a wider field and include not only those cases of massive pleural effusion complicating ascites due to ovarian fibroma and carcinoma, but also those due to cirrhosis of the liver and other causes of ascites. The mechanism of the pleural effusion is surely the same in all these conditions where the fluid in both the peritoneal and pleural spaces is exactly similar in all respects.

The suggestion that the fluid crosses the diaphragm through normal lymphatic channels seems most unlikely for the following reasons: (1) Although experimental studies have shown that the ascitic fluid can reach the subpleural lymphatics, they have not demonstrated how it can reach the pleural space. (2) It does not explain why the hydrothorax is usually on the right side. (3) If ascitic fluid can pass so easily into the pleural space through normal lymphatic channels, a hydrothorax should invariably accompany ascites; but Meigs's syndrome is rare compared with ovarian tumours causing ascites alone, and hydrothorax with ascites due to cirrhosis of the liver is rare compared with cirrhosis causing ascites alone.

In the days of therapeutic pneumoperitoneum, a complicating right-sided pneumothorax, due to a hole in the diaphragm and its serosal coverings, was not a very unusual complication.[2] A similar mechanism probably explains many cases of massive pleural effusion complicating ascites. The ascitic fluid, under positive pressure, can readily be sucked into the pleural space through a very small hole in the diaphragm and its serous coverings. Several such communications have been reported.[3–5] The important point is that these holes may be too small to be seen on ordinary macroscopic examination and require a special technique for their demonstration, even at necropsy.[5] Until these communications through the diaphragm are looked for in all cases of Meigs's syndrome, we shall continue to accumulate case reports without becoming any wiser about the mechanism of the syndrome.—I am, etc.,

Westminster Hospital Chest Clinic, London, S.W.1. PETER A. EMERSON.

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Hormone Treatment of Breast Metastases

SIR,—Although the Therapeutic Trials Committee of the American Medical Association made a very good accumulated statistology of 944 pre- and post-menopausal, hormone-treated breast cancer cases, and many well-known American authors took part in this investigation, one can draw quite different conclusions

from the 60 American investigators (July 2, p. 41). Since I read the original American paper, may I be allowed to make some comments?

Having found in 1932 that hormones—at that time insulin and oestrogens (androgens were not available before 1936)—could influence cancer cells which were kept alive with Warburg's manometric method, I saw for the first time a surprisingly good result with massive doses of oestradiol in a cervical cancer in a woman of 70 years, in the cancer department of the Hufeland Hospital in Berlin.[1,2] From 1937 on, in London, I took up clinical investigations with androgens in pre- and post-menopausal women suffering from breast cancer with and without metastases. Including the cases I have seen in St. Bartholomew's Hospital, Rochester, and St. Mary's Hospital, Paddington, there are more than 400 cases which have been followed up for five years and more.[3-7]

It can be predicted in each case whether androgens or oestrogens are to be preferred in metastatic breast cancer, by making investigations as to whether or not a normal mammary gland reacts strongly to the endogenous oestrogens before menstruation. Post-menopausal women will remember how their breasts behaved when they still had monthly periods. The mammary gland reacts to the ebb and flow of oestrogens some 400 times in a woman's life. It is a pity that here, as well as in America, so few gynaecologists examine the breast of their gynaecological patients. If surgeons inquired of their patients about the behaviour of the breast before and during a period, they would find out which of the two sex hormones was preferable in breast cancer after mastectomy or in metastatic breast cancer. Vaginal smears in the post-menopausal period are also very helpful. I cannot believe that oestrogens are always preferable in the post-menopausal age, and I have found that in a few cases they have detrimental effect, especially where women reacted before or during the menstruation with a hyper-normal, painful breast swelling.

By far the best method in the therapy of disseminated mammary cancer in my opinion is to use oestrogens and androgens alternately or even both together,[8] and to avoid oestrogens where it is certain that the mammary gland reacted strongly before and during a period. I would venture to reproach the American surgeons that they do not use thyroid hormone with the sex hormones, in a dosage which may even produce a slight degree of hyperthyroidism, for thyroid hormone changes, through histamine production, the enzymatic internal environment of a patient—and that is after all the main point.

May I close my remarks with a few words I spoke to Dr. Frank Adair in the Royal Society of Medicine on June 1 this year, when he detailed the results of 10,000 radical mastectomies he had performed during the last 40 years. Frank Adair was himself one of the 60 American authors on the Therapeutic Trials Committee. I told him that subthyroid people with very little histamine in their tissues were prone to breast cancer, whereas hyperthyroid or allergic people very seldom got it. His famous fellow American Dr. Leo Loeb stipulated the formula: the hereditary constitution of a person multiplied by a stimulus (and this stimulus may be chronic inflammation or some chemical substance) results in cancer.

$$c \times st = \text{cancer}$$

I would like to change the formula to:

$$tc\ (\text{thyroid heredity constitution}) \times st = \text{cancer}$$

The stronger the thyroid activity the rarer the cancer, and as the function of the thyroid gland decreases after 50 years (proved by histological examinations), and as the height of the epithelium lowers as the years go on, our task is to offer the breast tissue in all ageing people with a family history of cancer or thyroid anomalies, as well as women after mastectomy, irradiation, or with disseminated cancer metastases, as much thyroid hormone as possible—whether it is an operable or an inoperable case. At St. Bartholomew's, Rochester (the cancer centre for Kent), at least 200 people have been treated in this way after mastectomy, and also about 100 cases in St. Mary's, Paddington. It is amazing what large quantities of thyroid hormone cancerous women can stand, and only one in ten shows any undesirable heart reaction.—I am, etc.,

London, W.1. ALFRED ALEXANDER LOESER.

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Development of Live Polio Vaccine

SIR,—In spite of their happy ending, I am extremely concerned about the ethical position in respect of the experiments carried out by Dr. Hilary Koprowski, referred to in his lecture "Historical Aspects of the Development of Live Virus Vaccine in Poliomyelitis" (July 9, p. 85). It is alarming when he says, "This was the first public disclosure of oral administration . . . etc." What is more perturbing is his statement, "Because of its nature, knowledge of this trial was at first confined to Dr. Jervis, Mr. Norton, and myself. No one else knew of the study during the period between February 27, 1950, when the first child was fed with virus, and late January, 1951, when observation of the first series of 20 subjects was nearing completion and preliminary evaluation of the procedure indicated it was harmless."

In view of the large number of so-called experimental trials of various kinds at present being undertaken, is it not high time that some control be placed on individuals carrying out such trials on people who have not volunteered? The public are entitled to this protection.—I am, etc.,

Manchester, 9. D. E. JEREMIAH.

Imaginary Poverty

SIR,—There exists a common, well-defined mental aberration which I have never seen reported. The patient, who is tormented, has no insight, is not amenable to reason, and, as there are two delusional components, the condition qualifies as a psychosis. I call it Imaginary Poverty.

The patient, whose finances are, in fact, extremely sound, and who spends lavishly on luxuries, believes he cannot afford necessities. The second delusional aspect is an implied belief that life on this earth will continue indefinitely, and no capital must be realized for fear of compromising the security of this interminable future. The malady can afflict, of course, only the well-to-do, but is not confined to any one social stratum; incidence increases with age, and female cases predominate, though they are probably not more often afflicted than would be expected from their preponderance in the older age-groups. Often there are no dependants, and at demise the State is the chief beneficiary. Occasionally the delusion has been purposefully engendered by a hitherto disinterested relative who may be found, filled with belated solicitude and hovering, literally, on the doorstep during the

terminal illness, awaiting pronouncement of death. Usually there is no evidence of such a genesis.

These patients are invariably on one's N.H. list, as they "cannot afford to pay fees," and are exacting in their requirements. They often live alone, and spend their last few weeks in isolation and discomfort under the misapprehension that they can afford neither a private nurse nor a nursing-home. Occasionally, however, they face the prospect of nursing-home charges with astonishing equanimity. In general there is a readiness to spend on material things and a reluctance to pay for services and essentials, such as a good dietary. Costly outer garments, new furnishings, alterations to the house, and holidays abroad are allowable; underclothes, bed-linen, help in the house, and food are not. Whilst their abodes usually display every outward sign of affluence, in exceptional instances the diagnosis can only be made *post mortem*—that is, when their estate is published. In other respects they are sane, and I exclude those suffering from senile mental changes from the diagnosis.

The disease is to be distinguished from miserliness, or the enjoyable hoarding of riches without delusion of poverty; from avarice and cupidity, both of which the *Concise Oxford English Dictionary* defines as "greed of gain" and in which there is no such disproportion of values; parsimony, with which one associates the careful deployment of available resources; the true destitution of inevitable poverty; voluntary poverty as practised by some religions; and the fashionable poverty-*sois-disant*, or "one-downmanship." What is the aetiology of this penny-wise-pound-foolish attitude?

Case histories are numerous, and recent examples include an intelligent spinster dying of an obscure bulbar palsy and who knew the end was near. Her assets were in excess of £20,000, but she died disconsolate as I was unable to accede to her request for toilet-tissues "on the National Health." An 88-year-old spinster resident in an expensive nursing-home joined my list on account of "reduced circumstances" and died two months later with £4,000 in a current account. An elderly man, having boasted that his cruise ticket cost over £400, objected to paying a fee for the International Certificate and to paying one shilling for anti-cholera vaccine; he contracted an illness abroad from which he did not recover, leaving over £40,000. A rich widow, slowly dying, spent her last few days in the mental anguish of not knowing if she would live to receive the insurer's cheque in settlement of her claim for a burnt-out wireless receiver. A woman who avowed that an egg for breakfast was an extravagance which she "could not afford" immediately entrusted her daughter with the purchase of an antique priced at £20.

I know of no treatment for this illness and would be interested to hear of its prevalence elsewhere.—I am, etc.,

Worthing. A. W. BEATSON.

Aortic Incompetence in Ankylosing Spondylitis

SIR,—Having read Dr. R. S. Crow's article (July 23, p. 271), I thought the following case with a similar length of history might be of interest.

Mr. W. R., aged 59, first had ankylosing spondylitis of the dorsal spine diagnosed in 1938, and for this he has had two courses of deep *x*-ray therapy. He was reasonably well following this until October, 1959, when he first had severe angina, for which he now takes at least 25 glyceryl trinitrate tablets daily.

Clinically, he has a regular pulse, 70 per minute, blood pressure 140/55, and both diastolic and systolic aortic murmurs, but with no evidence of mitral valve disease. His spondylitis in recent months has also worsened, and the patient himself is convinced that the two conditions are closely related.

—I am, etc.,

St. Bartholomew's Hospital, London, E.C.1. J. A. PARRISH.

Immobilization of the Arthritic Hip

SIR,—Mr. T. T. Stamm (April 16, p. 1207) has written that it is impossible to immobilize a hip by any form of external fixation tolerable to the patient. Until recently I have believed this to be true. For nearly every joint it has been possible to develop a method of "active immobilization" which fixes the painful joint yet preserving the activity of the limb. For the hip I have proceeded for 10 years by trial and error, and until lately have not succeeded in developing a reliable method of immobilization. Lately I have been helped by Mr. Rex Davis, an ingenious and enthusiastic Melbourne prosthetist. He has now produced a light metal splint (see Fig.) based on Thomas's original ideas. This must be kept on for 10 weeks continuously, as follows: (1) Rest in bed for five weeks; twice daily get up on crutches, with no weight borne on painful hip. (2) After five weeks discard crutches and walk with splint on. (3) After five more weeks remove splint but do not bend hip.

A dozen patients who have used the splint (mostly at home) have remarked that the hip pain disappeared as soon as it was immobilized. Four weeks after removal of the splint a few degrees of painless movement have returned; but flexion must not be actively sought. In every patient it seems that the arthritic process has gone into remission—I cannot say for how long.—I am, etc.,

East Melbourne, Australia. MICHAEL KELLY.

Avulsion of Nails

SIR,—One sometimes sees an ugly mass of scar tissue with a bit of nail on it, where a whole nail should be, and I have just seen such a thumb, where the nail was removed years ago. We were certainly taught to split a nail and avulse the two sides rapidly.

I once removed half of my own big-toe nail with no pain, no bleeding, but it took nearly three hours to separate it from the nail bed. It grew perfectly again. It had been ingrowing. It would take far less time with an anaesthetic, but why is it usually done so rapidly as to tear the bed?—I am, etc.,

Farningham, Kent. H. M. DENHOLM-YOUNG.

High-pressure Salesmanship

SIR,—As a medical representative for a leading British pharmaceutical company, I have followed with great interest the correspondence in your columns on "High-pressure Salesmanship." I cannot but wonder whether the opinions expressed represent a general uprising of the medical profession or are simply those of a substantial minority. Although I can understand and sympathize with these views, I yet continue to receive, with rare exceptions, a courteous welcome from the doctors on whom I call.

Certainly, if mailing and representation are now sometimes being taken to excess, the doctors must take at least a share of the blame, for they have let such tactics

succeed. Every company exists to make a profit, and expends nothing on publicity that it does not expect to recoup with interest. The companies who mail daily and call every six weeks have so far succeeded, and nowhere is opposition to them greater than among the mass of representatives, lest the medical profession tar us all with the same brush and banish us from their surgeries.

If the problem has now reached serious proportions, surely the solution must lie not in *ad hoc* arrangements by the more hard-pressed doctors but in some reasonable code of conduct agreed on between the B.M.A. and the Association of British Pharmaceutical Industry. —I am, etc.,

Newton Aycliffe, Near Darlington. NORMAN BURDEN.

Artificial Insemination

SIR,—At least two Government committees have rushed into print and given conclusions on insufficient data. First, the Wolfenden Committee, and now the Committee on A.I.D. (July 30, p. 379). In both these cases not enough study or research on the problem has been done to provide material for adequate judgment. Previous committees on artificial insemination have sanctioned A.I.H., but experience with marriage guidance cases has shown that it is the impotent, immature, and inadequate husband, although fertile, who requires artificial aid. The cases of A.I.D., although generally potent and mature men, have yet by reason of war wounds, mumps, etc., become infertile. Which of the two are likely to become better husbands and better fathers ?—I am, etc.,

London, W.1. A. TORRIE.

Recruitment and Training of Nurses

SIR,—At this hospital 30 badly needed beds are closed due to shortage of nursing staff. This state of affairs is reduplicated all over the country. I feel that besides an increase in pay this problem will not be solved until the nursing service is organized on the following lines.

Male and female staff, aged 18 to 45, should be recruited by hospital matrons and Ministry of Labour and Ministry of Education representatives. A matron who has plenty of staff will of course be more choosy than one who has not. They should be called nurses, not aides or orderlies, and should have a simple course in first aid, bedmaking, urine-testing, oxygen-administration, etc.

Matrons should select from the rank-and-file the most promising personnel for further education in the more specialized techniques, such as midwifery, children's nursing, acute surgical nursing in the pre- and post-operative unit, maternity and mental nursing, etc. There should be refresher courses paid for by the State for personnel going into administration or to sister and staff-nurse posts. Education should be linked to a university—for instance, sister tutors could be called readers in nursing. Badges of rank should be worn on the arm—for example, probationer nurse, nurse, senior nurse.

A nurse can stay at any grade which suits his or her ability. Hospital management committees should call for volunteers, from those seeking promotion, for vacancies for the various courses and pay for them. Nurses returning to duty after prolonged absence due to marriage may need special refresher courses.

It does not seem very much use building new hospitals until this basic nursing problem has been solved. I know that none of these suggestions are original, but they comprise a selection of the most practical ideas put up by others.—I am, etc.,

Bevendean Hospital, Brighton, 7. F. E. CAYLEY.

Obituary

H. SANDEMAN ALLEN, O.B.E., T.D., M.A. M.B., B.Ch., F.R.C.S.

Mr. H. Sandeman Allen, a well-known gynaecologist and obstetrician in the Cheltenham district, died suddenly on June 30 only a week before he was due to retire from his hospital appointments. He was 64 years of age.

Harold Sandeman Allen, " Sandy " as he was always called by his many friends, was educated at Greshams School, Holt, and studied medicine at Cambridge and St. Thomas's Hospital. After qualification in 1923 he was house-surgeon at the Royal Northern Hospital. He then returned to St. Thomas's as registrar to the obstetrical and gynaecological departments and later he became obstetric tutor and chief assistant to the gynaecological department. He gained his F.R.C.S. in 1928.

He went to Cheltenham in 1930, and, as was the custom in those days, he entered a general practice. He was soon appointed assistant surgeon to Cheltenham General Hospital. Some three years later he was appointed to the full staff and carried out a busy surgical practice in Cheltenham and in a large surrounding area. At the outbreak of the second world war he joined up as a territorial and became a Lieutenant-Colonel in command of a field ambulance. He was awarded the O.B.E. for his military services, and in 1950 the Territorial Decoration. After the war he returned to Cheltenham, and from then on gave his full time to his consultant work, becoming more and more occupied with gynaecology and midwifery. On the advent of the Health Service he was appointed consultant gynaecologist to the North Gloucester clinical area, a post he held until his death.

Sandy was a man of many interests. He was a leading figure in the Masonic world, in which he held several high offices, senior medical officer to Cheltenham racecourse, a keen and active member of the local golf club, of which he was president, an enthusiastic and skilful amateur carpenter, and a man who enjoyed his social activities among a wide circle of friends. His unexpected death was a profound shock to his colleagues, and, coming as it did so near his retirement, has caused great sorrow in all the hospitals in which he worked. He was much loved and respected by all who worked with him, and was an example to us all in his scrupulousness, his absolute honesty, and his unfailing punctuality and precision in all he did. The thought of retirement was never pleasant to him, and, while his sudden death seems so tragic, there is a feeling that he had achieved his life's work and yet was spared the inactivity of old age which he had always regarded as such an anticlimax after a very busy life.

He is survived by his wife and two grown-up daughters, to whom we extend our deepest sympathy in their tragic loss.—R. G. C. H.

M. D. B. TONKS, M.R.C.S., L.R.C.P.

Dr. M. D. B. Tonks died in retirement at Aberdeen on June 5. He was 69 years of age.

Myles Denison Boswell Tonks qualified from the London Hospital in 1915. After the first world war he settled in general practice in Rochester and stayed there until he was bombed out in the second world war. He was honorary secretary of the Rochester, Chatham, and Gillingham Division of the B.M.A. from 1921 to 1934. He moved to Watchet, Somerset, in 1942, and remained in practice there until he retired in 1958.

R. J. L. writes: The sad loss of Myles Tonks was a great blow to all his old patients and friends. We had sincerely hoped that he would be given more than just two years in

which to enjoy the fishing and painting at which he was such an expert and which he loved so much. I was privileged to be his junior partner in his latter days in general practice and I have never known a better friend, a wiser doctor, or a man whose high ideals were such a shining example both to me and to everyone who came in contact with him. When he decided to retire from general practice I sincerely missed his sagacity in matters both great and small. He had battled for some years with ill-health, and although he dispensed good advice to his patients he never spared himself in their interests. Our deepest sympathy goes to his widow and three daughters in their bereavement.

W. H. CHESTERS, M.B., B.S.

Dr. W. H. Chesters, who practised in Bromley, Kent, for 46 years until he retired in 1954, died at his home in Bedford on July 3. He was 81 years of age.

Walter Horsfall Chesters was born on July 28, 1878, in the West Indian island of Montserrat, where his father, the Rev. F. S. Chesters, was a missionary. Educated at Kingswood School and London University, he graduated M.B., B.S. in 1908. He then entered general practice in Bromley. During the first world war he held an appointment as an anaesthetist at the Royal Herbert Military Hospital, Woolwich, and was also assistant medical officer to Biggin Hill R.A.F. Station. He managed to carry on his practice at the same time. During 40 years' membership of the B.M.A. he was secretary of the Bromley Division in 1922–3, and chairman during 1928–31.

Dr. Chesters had deep religious convictions, and was for 24 years vicar's warden at St. John's Church, Bromley. Music was his great interest. His mother, Marion Horsfall, was trained at the Stuttgart Conservatorium under the famous professors Lebert and Stark, and she transmitted much of her own musical genius to her eldest son. He was equally at home with the piano or the organ, and was especially fond of Brahms. It meant much to him that his wife and daughter both possessed fine voices and were able to collaborate with him in making music on the concert platform. The Bromley Musical Festival, of which he was a founder-member and for many years chairman, owes much to his kindly leadership and advice. He married Esther Maud, the youngest daughter of Mr. Benjamin Stephens, of Monmouth, and she survives him, together with a son and a daughter, and a son-in-law who is also a doctor.

A. C. HADDOW, T.D., M.B., Ch.B.

Dr. A. C. Haddow, for many years a general practitioner in Leeds, died on July 8. He was 73 years of age.

Archibald Campbell Haddow was born on March 13, 1887, the son of Dr. John Haddow, of Glasgow. He was educated at the High School, Glasgow, and Glasgow University. He graduated M.B., Ch.B. in 1910, and went to Armley, Leeds, in 1913. He remained in general practice there until his retirement last year. He was a keen territorial and was medical officer to a battalion of the Duke of Wellington's Regiment. He served with distinction with this and other units in France and Belgium throughout the first world war. On his return he was attached to the Divisional Train, Army Service Corps, and later joined the Divisional Signals of the 49th Division, where he remained for many years as a most efficient and popular medical officer.

When the 147th Field Ambulance was re-formed in Sheffield, Colonel Haddow was given command and brought it up to a high degree of training. Soon after the outbreak of the second world war he was appointed A.D.M.S. to the newly reconstituted 46th Division and was promoted colonel. Here he did much in building up the new medical units. He later commanded the 28th General Hospital and went out to Iraq. He was demobilized in 1944 from Oxford. Later he did a term as Honorary Colonel of the 49th Divisional Medical Services. He held the Territorial Decoration with bars.

He was also surgeon to the Armley Division of the St. John Ambulance Brigade for 40 years, and was appointed a Serving Brother of the order. His retirement was made the occasion for an address and a presentation to mark his long and valued service.

Dr. Haddow was a regular attender at the meetings of the Leeds and West Riding Medico-chirurgical Society for many years, and filled the office of president with distinction and success. He was a good, conscientious, and able practitioner greatly devoted to his patients, who thought most highly of him and much appreciated his kindness and painstaking attention. He got on extremely well with his colleagues, and placed freely before them his great experience and advice. He had a great sense of humour and his many dry and witty remarks and anecdotes charmed his hearers.

Dr. Haddow will be greatly missed, but will long be remembered by all those who were fortunate to know him. He leaves behind a widow and a son, to whom our deepest sympathy is extended.—J. E. R.

J. P. BLIGH, M.B., Ch.B.

Dr. J. P. Bligh, who had been in active general practice in Liverpool for over 50 years and had succeeded to a practice established by his father in 1864, died on July 13. He was 81 years of age.

John Patrick Bligh was born in Liverpool on October 15, 1878. He graduated M.B., Ch.B., Victoria University of Manchester, in 1903, and M.B., Ch.B., Liverpool, in 1904. This was at the time when Liverpool University was granted its charter, and he took great pride in being one of Liverpool's first medical graduates. In due course he succeeded to the practice his father had established in Liverpool so far back as 1864. He became a very busy general practitioner, and was medical officer to the Brownlow Hill Institution and to many of the colleges and convents around Liverpool. He held a prominent position in Roman Catholic circles and numbered among his patients many of the clergy and members of religious orders.

In his younger days Bligh was a keen sportsman, and right to the end he used to enjoy his round of golf. Until his last brief illness he carried on his practice, and, despite his years, retained his mental and physical vigour and youthfulness of spirit to a remarkable degree. This he attributed to his close association with young people, with whom he was a great favourite. He leaves a widow and four sons and four daughters. One son is a doctor in practice in Liverpool.

R. D. H. writes: Although I knew John Bligh only in the last 20 years of his life, I never ceased to wonder at the apparent perennial youth of the man. His puckish sense of humour, his love of children, and his delight in games of all sorts no doubt accounted for much of this everlasting youth. He had many grandchildren, but all children loved him, so that he was "Grandad" to a very large number who were not related to him. He had played many games as a young man, and until quite recently he enjoyed his game of golf, while billiards and snooker in his own home gave him an opportunity to extend the hospitality for which his household was justly famous.

He retained to the end an interest in all that is new in medicine, and, while deploring the cost of some of the newer pharmaceutical preparations, he was always ready to use them after subjecting his colleagues to a searching inquiry about their value. Although troubled by deafness in his later years, he never appeared to be handicapped by this disability. Probably his outstanding characteristics were his essential humility, his dislike of all things pompous, and his tolerance towards all shades of opinion. A staunch Catholic, one of his closest friends was an equally staunch Protestant from Ulster. He radiated tolerance, so that one left his home full of good humour and feeling relaxed.

He was supported in his work by a devoted wife, herself a member of an old medical family, who shared with him

the ups and downs of a busy medical life for almost fifty years. They remained in the heart of Liverpool, in the centre of the practice, throughout the worst days of the blitz, and never ceased to give care and comfort to all those who sought their aid, whether or not among members of the practice.

To Mrs. Bligh and their eight children, the eldest son being the third generation to be medically qualified, we extend our deepest sympathy.

EDITH M. D. INGLIS, M.B., Ch.B., D.O.

Dr. E. M. D. Inglis, a notable figure in Kilmarnock, died at her home there on July 24. She was 62 years of age.

Edith Marion Douglas Smith graduated M.B., Ch.B. from St. Andrew's University in 1922. She took the Diploma in Ophthalmology at Oxford the following year and joined the staff of the Oxford Eye Hospital. In 1925 she married the late Alexander Inglis, a well-known Kilmarnock lawyer, and from then on kept up her interests in a voluntary capacity in Kilmarnock Infirmary. She also served with the British Red Cross, and was created an honorary member of the society. During the second world war she continued lecturing for the Red Cross; acted as medical officer to the Women's Land Army; and gave anaesthetics at Kilmarnock Infirmary. It was in keeping with her principles that women should be prepared to shoulder their responsibilities in the community that she accepted nomination and was elected to Kilmarnock Town Council, which she served until her husband's premature death.

Subsequently she returned to full-time work as an eye specialist, this time serving the whole of Ayrshire. She was a skilful surgeon and a wise physician. In addition many hundreds of children throughout Ayrshire had the benefit of her skill through the school eye-clinics. She was notably kindly and considerate in a task which calls for such qualities in a high degree. In spite of a prolonged illness over the last two years she carried on courageously until only two months before her death. She will be missed in many spheres of life.

Among other activities she was a former member of the Bach Choral Society at Oxford and the Kilmarnock Choral Union. It was also typical in a many-sided personality that she practised the tenet of *Mens sana in corpore sano* and played golf enthusiastically, while she supported organizations like the National Trust for Scotland. At the same time she was essentially a family woman who brought up two daughters and a son in the fullest sense of family life. Her husband died while the children were still at school, and it was Dr. Inglis who saw each of them through a distinguished university career.—W. O. G. T.

Sir ERNEST ROCK CARLING, LL.D., M.B. F.R.C.P., F.R.C.S., F.F.R.

The obituary of Sir Ernest Rock Carling was published in the *Journal* of July 23 (p. 313).

Dr. A. J. SHINNIE writes: I have read with warm appreciation the many tributes paid to my dear friend Sir Ernest Rock Carling by distinguished members of our profession, but I feel it would have been his wish that I, who had known him since 1912, should not remain silent. His senior in the Westminster Hospital in those far-off days was Charles Stonham, from whom he learned much and of whom he always spoke in revered admiration. A contemporary in student days was the late Arthur Evans. Both were destined to add distinction as surgeons to their own hospital, and did they not treasure the football caps they had won in defending the fair name of Westminster in the inter-hospital games!

All his life he lived for Westminster Hospital. It was his great love and the new building, opened in 1939, was his child. He was, and ever will be, regarded as its central pillar. For almost 50 years I enjoyed his friendship, and many friends and relatives of mine have benefited from his surgical skill displayed with such gentleness and kindness. Always neat and immaculate, his 83 years were belied in his ever alert mind and wiry physique. He spoke with the voice of authority on so many aspects of scientific knowledge and we treated his opinions with enormous respect. He was a founder member of our City of Westminster Old People's Welfare Association, and his address to us at an annual general meeting will always be remembered.

During the war he gave our B.M.A. Division (Westminster and Holborn) a fascinating account of a visit to Russia with a few surgical colleagues. What they were allowed to see of surgical techniques excited admiration, but at bayonet point they were barred from entering some of the museums. It was the dangerous period of the Russian convoys.

He and I were members of the Westminster Medical School Council for the past 30 years and more, and for still longer members of the Society for the Relief of Widows and Orphans of Medical Men. He was treasurer and I usually sat beside him. At our quarterly meeting only two days before he died he was the same alert and business-like treasurer. Little did we think that within the same year our two most distinguished honorary officers, Sir Robert Young and Sir Ernest Rock Carling, would be taken from us. Let us all offer our grateful thanks for the friendship of one whose whole life was dedicated so selflessly to the service of mankind.

Medical Notes in Parliament

QUESTIONS IN THE COMMONS

Report on Maternal Deaths

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on July 18, in the light of the disclosure in his department's Report on Maternal Deaths, 1955–7,* that 41% of the 861 deaths expertly assessed were attributable to neglect and mismanagement and could have been avoided, what new steps he intended to take to protect the lives of women in childbirth. Mr. D. WALKER-SMITH replied that he did not think that these figures carried quite the implication Mr. Robinson suggested. The report covered the second three years of a continuing investigation of the factors contributing to maternal deaths, and by promoting the study of those which were avoidable was itself an important contribution to the measures taken to bring about an improvement. He was glad to say that this second report contained ample evidence that a considerable improvement had been achieved.

Mr. ROBINSON described the report as extremely disturbing and providing the most powerful argument for the early implementation of the Cranbrook Committee's recommendation about more carefully controlled obstetric lists. Mr. WALKER-SMITH said that the recommendation was under consideration in consultation with the medical profession.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said the report stated specifically that domiciliary and hospital midwifery could be severely criticized—that women who died in childbirth had suffered from heart disease, and no one had examined the heart before confinement, and that people unfitted to do caesarean sections had done them. Mr. WALKER-SMITH: In so far as the report draws attention to avoidable factors it does a public service, and we shall seek to ensure that those factors are avoided in future. At the same time one should keep the context in view. Over the three years covered by the report, more than two million women were safely confined, and in this decade we had succeeded in reducing the figures of maternal mortality from 0.87 per 1,000 in 1950 to 0.38 per 1,000 in 1959, a reduction of more than half. These are figures which I think would arouse world envy and excite the emulation of most countries.

*See p. 456 for a summary of the report.

Medical Treatment of Foreigners

Dr. ALAN GLYN (Clapham, Con.) asked how many foreigners belonging to countries with which this country had no reciprocal arrangements had received free treatment under the Health Service in the last twelve months; and what was the estimated saving, including any administrative costs, that would accrue to the Exchequer if they were refused free medical treatment. Mr. WALKER-SMITH replied that information about numbers was not available. Having regard to the probable cost of any scheme for identifying foreigners, he doubted if any net saving would accrue.

Dr. GLYN, advocating the extension of reciprocal arrangements with other countries, suggested that one of the best ways of achieving it would be to stop free treatment to nationals of countries who did not have reciprocal arrangements. Mr. WALKER-SMITH would not accept this as the best method of obtaining reciprocity. It was better to proceed on a basis of good will. The cost was relatively small. Efforts were made to check abuses. But in the second half of the twentieth century it was desirable not to fall below the standard of mediaeval monasteries, which asked the sick traveller not whence he came or whither he went, but sought to help and heal him.

Student Entry to Medicine

Mr. L. PAVITT (Willesden, West, Lab.) asked the Minister for the number of full-time students entering university institutions for the first time in the faculty of medicine for the years 1954–5 and 1958–9; and if he was satisfied that the current supply of newly qualified doctors was sufficient to staff the Health Service.

Mr. WALKER-SMITH stated that according to his information the number of students entering medical schools in Great Britain was about 2,100 in 1954–5 and about 1,900 in 1958–9. The Willink Committee, reporting in 1957, had suggested a reduction in student intake of about 10% as soon as practicable. The Royal Commission on Doctors' and Dentists' Remuneration, which reported last February, expressed the view that the supply of candidates for training as doctors was reasonably close to requirements.

Mr. PAVITT drew attention to Professor Jewkes's comments on the slowing down of the intake into the faculty of medicine, and said that it was desirable to reduce large lists among general practitioners to the national average, which would require more doctors. Mr. WALKER-SMITH replied that the majority report said that the supply of candidates for training as doctors was reasonably close to requirements.

Psychiatric Research

The Parliamentary Secretary, Miss EDITH PITT, stated in reply to Mr. KENNETH ROBINSON on July 22 that the estimated annual cost of the two psychiatric research units recently established by the Medical Research Council was approximately £14,875. The Council's total expenditure on psychiatric research in the current financial year would amount to about £200,000, which represented about 4.7% of their estimated total expenditure.

Research on Arthritis and Rheumatism

Mr. A. E. HUNTER (Feltham, Lab.) asked the Minister on July 25 what was the amount spent in 1958 and 1959 on medical research into the causes of arthritis and rheumatism; and what future plans he had for enlarging this research work. Miss PITT told him that the Medical Reseach Council's total expenditure on research into the causes of arthritis and rheumatism amounted to approximately £37,000 in 1958 and £46,000 in 1959. The Council's programme of research on rheumatic diseases had expanded considerably in the last two years, and support would be given to new investigations whenever the opportunity occurred. In addition to the work done by the Medical Research Council research was undertaken at Health Service hospitals and in university medical departments. In these and other institutions some research was also supported mainly or entirely by voluntary organizations, such as the Empire Rheumatism Council. Figures for the cost of these research activities were not readily available.

Russian Multiple Sclerosis Vaccine

Sir ARTHUR VERE HARVEY (Macclesfield, Con.) asked what steps had been taken to test the Russian vaccine for the treatment of multiple sclerosis. Miss PITT answered that no steps had been taken in this country because the advice of the Medical Research Council was that there was not sufficient evidence that this vaccine was of any benefit; there was therefore no reason to believe that the vaccine was worthy of intensive study or clinical trial.

Polio Vaccination of Children

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked for the number of children, aged 15 years and under, who in 1958 and 1959 received their first injection of Salk vaccine, the percentage returning for a second injection, and the percentage returning for a third injection. Miss PITT informed her that by the end of 1958, 7,083,000 children had received at least one injection, and 96% of these had at that date also received their second injection. By the end of 1959 the corresponding figures were 9,580,000 and over 99%. Figures of third injections were not available for children separately; but 86% of those persons who by October 31, 1959, had had their second dose had by June 30, 1960, had their third. She also stated that at the end of June over 99% of children aged 15 and under who had been given a first injection had returned for further injections.

Bleaching Agents in Flour

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) asked the Minister of Agriculture, Fisheries, and Food what bleaching agents or improvers were in use for the treatment of flour since agene was forbidden; and what was the evidence that these were not also harmful to health. Mr. J. HARE stated that the bleaching agents and improvers in use were chlorine dioxide, potassium bromate, potassium persulphate, benzoyl peroxide, nitrogen dioxide, chlorine, and sulphur dioxide. He understood that the Food Standards Committee's Report on Bread and Flour, which he expected to receive soon, would include a study of the evidence.

Accident Proneness

Mr. R. GRESHAM COOKE (Twickenham, Con.) asked the Minister of Transport on July 27 what progress he has made in consultations with the insurance companies about accident proneness; and whether the companies would be able to draw statistical conclusions. Mr. E. MARPLES stated that this matter was discussed at a meeting on July 7 with the chairman of the British Insurance Association, the chairman of Lloyds, and others. They noted a number of practical difficulties which would arise in trying to use insurance records. A small committee of those concerned would examine this whole question. No quick results could be expected.

Medico-Legal

CURABLE INCAPACITY FOR INTERCOURSE

[FROM OUR LEGAL CORRESPONDENT]

On May 18, Mr. Justice Phillimore granted a decree nisi of nullity to Mr. Walter Ubaldo Gaboli, of Mount Park Crescent, Ealing, on the grounds that his marriage had never been consummated owing to the incapacity of his wife (*The Times*, May 19).

The parties were married in February, 1947, by the rites of the Roman Catholic Church, and lived together until February, 1959, when the husband left the matrimonial home. The medical evidence showed that the wife had a

physical impediment to the consummation of the marriage, but this impediment could be removed by a minor operation. The wife stated in evidence that she was willing to undergo that operation if her husband returned to her, but the court held that her offer was not genuine. On this view of the evidence the court rejected the submission of the wife's counsel that she ought not to be held incapable of consummating her marriage. The ecclesiastical courts required proof that incapacity was incurable by art or skill, but for many years the courts had regarded an impediment as incurable if the party suffering from the impediment was not prepared to undergo the appropriate treatment. After considering questions of approbation and delay in bringing proceedings, the court granted a decree nisi.

CANCER ALLEGATION AGAINST TOBACCO FIRM

[FROM OUR LEGAL CORRESPONDENT]

An American cancer patient, Mr. Otto Pritchard, aged 61, has lost his action for $1,250,000 (about £450,000) against the Liggett and Myers Tobacco Company (*The Times*, May 5). Mr. Pritchard has given notice of appeal.

Mr. Pritchard contracted cancer as a result of which his right lung was removed in 1953. He brought an action in the Federal district court in Pittsburgh claiming that his cancer was the result of smoking a brand of the company's cigarettes for many years. Dr. Leo Garland of the Stanford University Medical School gave evidence that available scientific evidence failed to establish an indisputable connexion between cigarette-smoking and lung-cancer. The judge held that no substantial evidence had been offered to support a verdict against the company on any theory of negligence, and on May 4 directed the jury to return a verdict for the defendants.

Even if it were possible to establish a definite causative link between the plaintiff's lung-cancer and a particular brand of tobacco, it is most unlikely that an action in negligence could succeed against the manufacturer. If it were proved that tobacco-smoking in certain quantities caused lung-cancer, the highest duty which could be imposed on a manufacturer would be to print warning notices on cigarette packets. But even in the absence of such warning it is unlikely that an action would succeed, as the defendant manufacturer would plead that the plaintiff smoker took the risk of smoking upon himself, so that the defendant would have the benefit of the maxim *Volenti non fit injuria*. The success of this defence would, however, depend on the ability to prove that the plaintiff knew of the risk at the time he indulged in the harmful smoking, which might be some years ago. An alternative defence would be contributory negligence, which, if successful, would result in reduction of damages: this defence also would depend on the knowledge of the plaintiff.

CORONERS' CASES

Death from Mountain Exposure

A healthy athletic youth, aged 18, died on April 13 from exposure whilst on a course at an Outward Bound Mountain School in Cumberland. Anthony Titley was one of a party of boys that set out, on April 11, for a three-day mountain expedition under the leadership of one of the school's instructors. Very bad weather, with heavy rain and cold winds, was encountered on the second day. Another boy in the group was obviously suffering from the effects of fatigue and the instructor decided to escort him back by an easier route, Titley being left in charge of the remainder. The appalling weather conditions forced the boys to shelter in a gulley near the top of Esk Hause, a high pass near Scafell Pike. They descended what later proved to be the wrong path and after half an hour two of the boys, including Titley, complained of cramp in the legs. At this point the party again split. Two remained with Titley and the others went on to get help. Titley became weak and collapsed and his condition rapidly deteriorated. By the time the rescue party reached him he failed to respond to artificial respiration, and on removal to the nearest farmhouse he was found to be dead.

At the resumed inquest at Whitehaven on April 27 the pathologist, Dr. A. C. F. Ogilvie, said that Titley was a tall thin boy and he had been in good health. Death was due to heart failure in consequence of exposure. The warden of the school told the coroner that this was the first death amongst 30,000 boys who had passed through the five Outward Bound Schools. A verdict of death from natural causes was recorded (*The Times* and *Yorkshire Post*, April 16 and 28).

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on July 9 the following degrees were conferred:

D.M.—D. W. K. Kay.

B.M.—D. M. Hill, J. Hodgson, R. E. Sadgrove, P. R. Wilson, C. Williams, R. L. Carter, D. J. Lane, G. M. R. Smith, W. L. Armstrong, J. L. Lane, A. J. Sandford, J. G. C. Surridge, D. G. Evans, C. W. K. H. Greaves, J. Brostoff, J. M. Rice Edwards, M. J. Parkinson, R. M. P. Reynolds, C. G. Jones, Celia Harvatt, Giovanna C. F. Karlsbad, Ann-Mary G. Lewis, P. G. Lynch, P. S. Vickers, *C. W. Burke, *Irene M. Jolles, *D. Barnett.

*In absence.

In Congregation on July 21 the honorary degree of D.Sc. was conferred on Professor A. N. Richards, Professor Emeritus of Pharmacology in Pennsylvania University.

The Board of the Faculty of Medicine has co-opted Dame Janet Vaughan, Principal of Somerville College, for the statutory period of two years from the first day of Michaelmas Term, 1960.

UNIVERSITY OF EDINBURGH

Dr. J. P. Duguid, Senior Lecturer in Bacteriology, has been admitted to the status of Reader, with effect from October 1, 1960.

Dr. R. H. Girdwood, Reader in Medicine, has been admitted to membership of the Senatus, with effect from October 1, 1960.

Honorary status as Honorary Lecturer in the Department of Pharmacology has been conferred on Dr. J. A. Loraine, a member of the staff of the Clinical Endocrinology Research Unit, and as Honorary Senior Lecturer in the Department of Medicine on Dr. J. McC. Murdoch.

Dr. D. J. McAuliffe has been appointed Lecturer in the Department of Ophthalmology, and Dr. W. A. Barr, Assistant in the Pregnancy Diagnosis Laboratory.

Dr. Helen A. Wright resigns from her appointment as Senior Lecturer in Bacteriology on September 30, 1960.

At a Graduation ceremonial on July 20 the following degrees and diplomas were conferred:

M.D.—B. Bendkowski, [1]S. G. F. Wilson.

CH.M.—[1]G. F. Murnaghan.

PH.D.—*In the Faculty of Medicine:* J. F. Lamb, M.B., Ch.B., B.Sc. M.B., Ch.B.—P. J. Abernethy, J. G. Adamson, C. I. Aitchison, F. A. Ala, F. Alcock, D. H. T. Bain, Annis H. Belbin, H. Berfield, I. J. Black, W. M. Bowden, A. W. Brewis, Margaret L. Brownlee, Sylvia A. Camp, R. J. Campbell, B. Canavan, [2]Isobel R. Card, Eleanor R. Chalmers, Philip Cheh See-yave (formerly Philippe Sow Chee Seeyave), D. J. Clark, I. G. Clark, D. J. Clarke, M. Cooper, G. N. Crookes, D. Dalrymple-Smith, Sheila M. B. Donald, M. L. Dorfman, W. H. Duthie, N. St. J. P. Dwyer, Jenny Eastwood (née Lucas), M. A. Eastwood, J. N. Edgley, T. E. Escott, K. W. Fairhurst, R. H. Farrow, D. M. Flynn, [2]W. L. Ford, R. E. Fraser, C. A. S. Galloway, J. M. D. Galloway, Mary W. Gibson, Elizabeth D. Glover, Janet M. Gray, Yvonne H. Green, W. Groundwater, Bridget M. Hackett, J. I. Hall, D. J. Hand, Elizabeth Hardisty, Pauline M. Hark, R. T. Hoohlo, B. C. Hovell, J. K. Howard, N. A. Hutchinson, Jean M. Hynd, A. H. Ibrahim, A. S. Jackson, Patricia M. James, I. W. Jamieson, W. P. U. Kennedy, Janet A. King, Sybil F. Kinghorn, Marion J. Lee, J. Lewis, S. Louw, Phyllis M. Lundie, A. A. A. McCall, Flora E. MacGregor, Catriona MacIntosh, D. S. Mackay, G. H. Mackay, Isobel R. Mackay, D. MacLean, M. A. MacLeod, D. C. Macmillan, G. P. McMullin, Margaret A. McVicker, N. A. Malcolm-Smith, [2]G. E. Mawer, C. P. Mayers, T. Middlemiss, L. R. Morgan, C. J. Morris, Heather S. Morris, Mary Morrison, [2]J. F. Munro, Pamela Murray, E. C. Mutasa, G. C. Namsoo, Matilda M. Nelson, Rosalind M. Niven, Joanna M. Oliver, A. H. M. Osman, J. J. B. Petrie, G. E. Philip, J. R. Philp, R. F. Rintoul, M. A. H. Robertson, H. N. Rutherford, G. Sachs, W. A. Sharman, D. A. Shedden, Anne E. Shepherd, L. F. Slade, C. McG. Small, G. E. Smart, R. W. Smethills, B. H. R. Stack, G. D. Stark, J. Stuart, M. McD. Tellis, K. W. Thompson, D. J. Turner, G. E. D. Urquhart, D. J. P. N. Van der Minne, J. L. Waddell, A. C. H. Watson, Julie M. Whittle, W. H. Williams, Paul Ling Nam Yan.

[1]Highly commended for thesis. [2]With honours.

DIPLOMA IN PUBLIC HEALTH.—N. B. Akim, Frances M. Falconer, Margaret McI. Gilmore, K. E. A. U. Ground, A. D. Macdonald, A. D. McIntyre, Isabella R. Napier, D. M. Pendreigh, E. J. B. Simpson, R. G. Walker.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—J. J. Kay-Butler, Q. S. Moore.

DIPLOMA IN MEDICAL SERVICES ADMINISTRATION.—J. P. Sexton, M.B., Ch.B., J. B. Stolte, M.D., H. B. Viefhues, M.D.

DIPLOMA IN PSYCHIATRY.—*W. E. S. Kiernan.*
DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—*S. Ali, H. M. S. Bristol, S. Durvasula, J. T. Millar, M. K. Pai, C. P. Sinha, Tin Aung Swe, Win Kyin Taw, I. M. Rohatgi.*

The following fellowships, etc., were awarded in the Faculty of Medicine: *Ettles Scholarship and Leslie Gold Medal in Medicine, Mouat Scholarship in the Practice of Physic, Beaney Prize in Anatomy and Surgery,* and *Keith Memorial Prize in Systematic Surgery,* G. E. Mawer. *Scottish Association for Medical Education of Women Prize, James Scott Scholarship in Obstetrics and Gynaecology,* and *Dorothy Gilfillan Memorial Prize,* Isobel R. Card. *Buchanan Scholarship in Obstetrics and Gynaecology,* J. F. Munro. *Conan Doyle Prize,* R. T. Hoohlo. *Lawson Gifford Prize in Obstetrics and Gynaecology,* W. L. Ford. *Annandale Gold Medal in Clinical Surgery,* Pauline M. Hark. *Murdoch Brown Medal in Clinical Medicine,* Annis H. Belbin. *Royal Victoria Hospital Tuberculosis Trust Gold Medal,* J. K. Howard. *Graduate Research Fellowships,* H. C. Bethune, A. Das Gupta, R. A. Harkness, A. F. MacDonald, Elspeth M. Russell. *Shaw Macfie Lang Fellowship, Lewis Cameron Postgraduate Prize,* and *William Leslie Prize in Surgery,* W. J. Irvine. *Graduate Research Scholarships,* A. W. Dellipiani, S. Selwyn, R. A. Sleet, M. B. Smith. *Graduate Travelling Scholarships,* J. G. Collee, G. D. Forwell, J. C. Gould. *Gunning Victoria Jubilee Prize in Anatomy,* B. Mackay. *William Leslie Prize in Medicine,* I. W. Delamore. *Greig Medal for Tropical Medicine,* M. K. Pai.

UNIVERSITY OF LONDON

The title of Professor Emeritus of Surgery in the University has been conferred on Sir James Paterson Ross on his retirement from the Chair of Surgery at St. Bartholomew's Hospital Medical College; Professor Emeritus of Morbid Anatomy in the University on Professor Dorothy S. Russell on her retirement from the Chair of Morbid Anatomy at the London Hospital Medical College; and Professor Emeritus of Bacteriology in the University on Professor Wilson Smith, F.R.S., on his retirement from the Chair of Bacteriology at University College Hospital Medical School.

UNIVERSITY OF LIVERPOOL

In Congregation on July 2 the following degrees and diplomas were conferred:

M.D.—G. Barber-Riley, J. D. Bates, A. E. Goetzee, W. H. Parry, P. H. Wright.
CH.M.—J. K. McC. Rawlinson, [1]A. V. Forage.
M.B., CH.B.—[2]K. F. Edwardson, [2]P. A. Murphy, [2]Ann E. Rogers, [2]Mary B. Wallace, [2]Diana Wardle, M. Alltree, Susan Almond, R. D. Atlay, [1]J. M. Barry, Anne Bayley, L. A. Bergman, R. C. Bland, J. A. Blankson, S. N. Booth, W. J. Boyle, Angela M. S. Brown, P. C. Cann, Avril G. Clarke, M. Cohen, D. E. Cooksley, R. Corcoran, B. J. Crane, Averil O. Dring, G. E. Fawcett, W. J. F. Gollins, G. W. Griffiths, D. V. Hicks, I. W. Hughes, H. D. Kaufman, P. J. Keating, E. B. Krasner, M. J. Lipton, Maureen Macdonald, Judith D. Madgen, P. Mann, J. H. Martindale, D. L. Mathias, C. D. Matthews, T. C. Mayer, G. A. Meadows, Janis L. Mikitis, A. R. Morris, Jean C. Moulds, D. A. Ogbe, R. D. Ll. Parker, D. Pearson, P. A. Rainford, P. W. R. Smethurst, Vivienne S. Strang, C. H. Taylor-Robinson, J. B. O. Thomas, Angela V. Turner, W. A. Warburton, J. Webster, M. Webster.
[1]*In absentia.* [2]With second-class honours.
DIPLOMA IN PUBLIC HEALTH.—K. M. Allman, A. Blench, Mary R. Cardwell, J. Carswell, D. Felix Richards, H. Gordon, Margaret O. Harrison, Winifred M. Jones, Marjorie V. Jukes, P. Kearns, J. G. Kingan, R. F. McKnight, Mary T. Neale, P. P. Rowan, J. A. Taaffe.
DIPLOMA IN RADIOLOGY.—*Radiotherapy:* R. A. Mian, R. T. H. Shepherd. *Diagnosis, Part I,* A. McDermott. *Radiodiagnosis,* N. H. Crosby, H. G. P. Jones, A. Kumar, C. B. Moss, Ma H. Myint, V. A. Rogers.

UNIVERSITY OF BRISTOL

Drs. P. A. Evans, J. A. Hayes, and M. J. Lewis have been appointed Demonstrators in Pathology.

Dr. D. M. J. Burns has resigned his appointment as Tutor in Ophthalmology.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on July 14 Sir Stanford Cade and Professor Digby Chamberlain were elected as Vice-Presidents.

Sir Clement Price Thomas, Mr. C. Naunton Morgan, and Mr. Hedley J. B. Atkins were readmitted as members of the Council, and Mr. Humphrey G. C. Arthure was admitted as a co-opted member of the Council.

Dr. J. William Hinton, of New York, was admitted as an Honorary Fellow, and Professor J. H. Louw, of Capetown, was admitted as a Fellow of the College by election.

A resolution of condolence was moved on the death of Mr. Seymour Barling, past Member of the Council.

A Moynihan Lectureship was awarded to Professor J. F. Nuboer, of Utrecht, and Dr. W. S. Stiles was appointed Edridge-Green Lecturer.

The Gilbert Blane Medal for 1960 was awarded to Surgeon Captain C. P. Collins, R.N.

Vital Statistics

England and Wales in Second Quarter

The birth rate in the second quarter was 17.6 per thousand population, the highest rate for a second quarter since 1949. The death rate was 11.0 per thousand population. The figures for the second quarters of 1959 and 1958 were 10.6 and 11.0. The infant mortality rate was 20.2 per thousand live births. The previous lowest for this quarter was 20.7 recorded last year. In 1950 second quarter the rate was 27.8. The stillbirth rate was 20.3 per thousand live and still births; the corresponding figure last year was 21.3.

Infectious Diseases

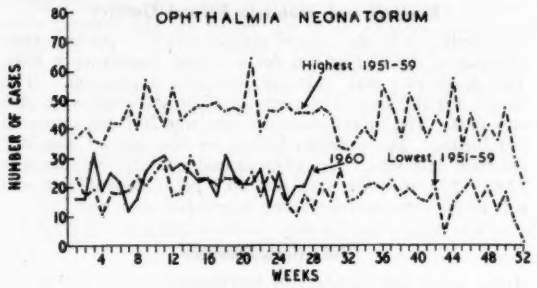
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

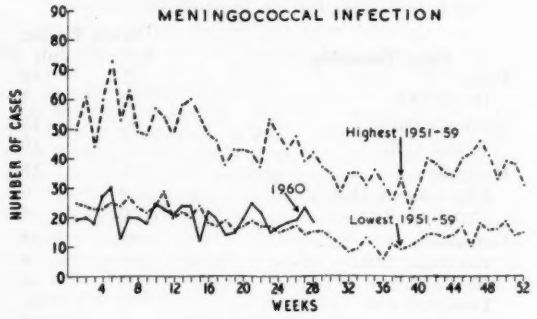
	Week Ending July 16	Week Ending July 23
Food Poisoning		
Essex	22	11
Ilford M.B.	10	7
Gloucestershire	12	10
Bristol C.B.	12	10
Hampshire	6	15
Christchurch M.B.	0	6
Droxford R.D.	0	5
Lancashire	48	64
Blackpool C.B.	23	4
Bootle C.B.	2	5
Liverpool C.B.	9	26
Manchester C.B.	4	8
London	21	22
Paddington	4	6
Sussex East	5	8
Eastbourne C.B.	1	6
Warwickshire	5	35
Birmingham	3	30
Yorkshire West Riding	18	20
Leeds C.B.	5	5
Acute Poliomyelitis		
Lancashire	0	3
Lincs (Lindsey)	0	2
Lincoln C.B.	0	2
Warwickshire	1	2
Birmingham C.B.	1	2
Dysentery		
Lancashire	130	120
Urmston U.D.	9	10
North Lonsdale R.D.	0	20
London	63	76
Hackney	3	11
Islington	15	15
Lewisham	19	15
Warwickshire	15	26
Coventry C.B.	5	14
Yorkshire West Riding	66	91
Leeds C.B.	13	17
York C.B.	3	20
Hemsworth R.D.	15	12
Glamorganshire	4	15
Cardiff C.B.	1	11

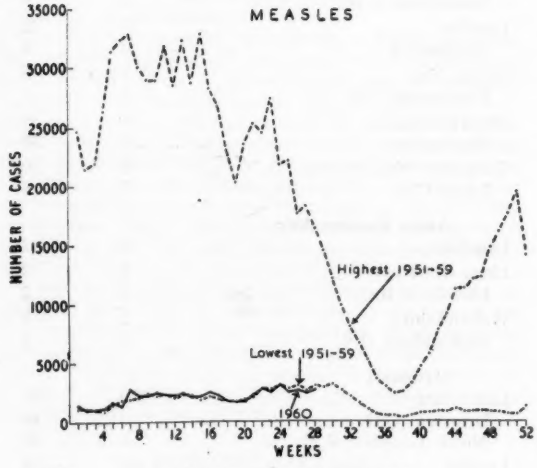
Graphs of Infectious Diseases

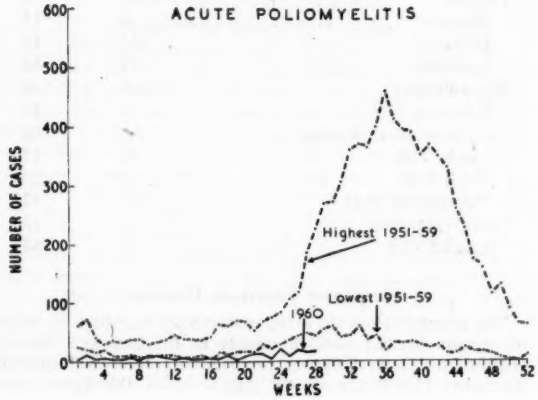
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for

1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 16** (No. 28) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	4	0		6	1	1	0	1
Dysentery ..	634	63	108	7	8	649	54	135	6	
Encephalitis, acute	6	1	0	0		3	1	0	1	
Enteric fever:										
Typhoid ..	1	0	0	0		3	0	0	1	4
Paratyphoid ..	3	0	0	0		10	0	0	0	
Food-poisoning ..	248	21	26	5		421	46	9	1	
Infective enteritis or diarrhoea under 2 years				13	26				8	35
Measles*	2,703	107	59	1	8	8,543	197	146	217	119
Meningococcal infection	18	1	14	0	1	16	0	3	1	1
Ophthalmia neonatorum	27	1	5	0		20	2	7	0	
Pneumonia† ..	145	7	71	0		178	11	96	2	
Poliomyelitis, acute:										
Paralytic ..	5	3	1	0	5	21	6	0	1	
Non-paralytic ..	11	2	1			22	2	1		
Puerperal fever§ ..	197	24	10	2		192	43	11	0	
Scarlet fever ..	422	21	43	7	16	781	45	53	23	26
Tuberculosis:										
Respiratory ..	421	47	66	11		446	60	88	24	
Non-respiratory	56	5	10	1		60	7	8	3	
Whooping-cough	1,627	113	129	5	43	685	29	62	8	45

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	1	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	1	0	0	0	0	3	0	1	0	0
Influenza	5	0	0	0	0	1	0	0	0	0
Measles		0	1	0	0		0	0	0	1
Meningococcal infection		0	0				0	0		
Pneumonia ..	361	24	13	10	2	304	20	18	9	8
Poliomyelitis, acute	1	0		0	0	5	1		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	57	5	5	0	1	63	2	4	0	2
Non-respiratory		2	1	0	0		0	0	1	0
Whooping-cough	3	0	0	0	1	0	0	0	0	0
Deaths 0–1 year ..	275	20	28	6	10	274	35	25	3	12
Deaths (excluding stillbirths) ..	8,424	643	485	90	121	7,834	614	457	94	145
LIVE BIRTHS ..	15,046	1284	576	272	433	14,431	1365	958	228	410
STILLBIRTHS ..	342	19	34			296	23	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Northern Ireland Health Service

The Northern Ireland General Health Services Board spent over £6m. in the year 1959–60—over 50% more than the figure for 1954–5, and 9% more than the previous year—it reveals in its *Twelfth Annual Report*. Pharmaceutical services cost 15% more than in 1958–9, general dental services 14% more, and eye services 10% more. The trend towards partnership practice can be seen from the fact that since 1953 the number of such practices almost doubled. Only 10,600 people transferred their doctor without changing their address—five years ago the total for the year was 20,000.

R.S.M. Awards

The Royal Society of Medicine has made the following awards:

Hughlings Jackson Lecturer and Medallist: Sir RUSSELL BRAIN (lecture to be delivered in February, 1961); *Sherrington Memorial Lecturer and Medallist:* Dr. D. E. DENNY-BROWN (lecture to be delivered in 1962); *Blair Bell Medallist, 1960:* Professor F. J. BROWNE; *Nichols Fellowship, 1960–1:* Dr. FRED BENJAMIN (Capetown University) for his work on "Glucose tolerance in dysfunctional bleeding at the time of the climacteric and in carcinoma of the endometrium"; *William Gibson Research Scholarship for Medical Women, 1960–2:* Dr. JEAN GINSBURG (research fellow, St. Thomas's Hospital Medical School) for her circulatory and metabolic studies.

Scientific Research Directory

The D.S.I.R. has issued its latest directory of *Scientific Research in British Universities*. It covers the academic year 1959–60. The information in the directory is collected by the British Council. The names of research workers and their subjects of research are catalogued by departments for all universities, university colleges, and associated institutions in Britain. There are name and subject indexes. The price is 25s. net (H.M.S.O., London).

"Current Medical Research"

The 12 scientific articles published in the *Report of the Medical Research Council for the year 1958–9* will be issued in booklet form under the title *Current Medical Research* on September 20. (H.M.S.O., price 3s. 6d., by post 3s. 10d.)

Henry Simpson Newland Prize, 1962

The subject of the essay for the 1962 Henry Simpson Newland Prize in Surgery (consisting of £100 and a medal) is "The Modern Management of Inflammatory and Neoplastic Diseases of the Left Colon and Rectum," and the competition is open to any graduate of any medical school within the British Commonwealth. Essays must be delivered to the general secretary—from whom details of the competition are obtainable—Federal Council of the British Medical Association in Australia, 135, Macquarie Street, Sydney, New South Wales, Australia, by January 15, 1962.

Members of Regional Hospital Boards

The following medical members of Regional Hospital Boards have been appointed:

Newcastle, Mr. D. C. Dickson, Professor G. E. M. Hallett, Dr. Theodore M. Cuthbert, Professor R. B. Green, Dr. R. G. Russell, Dr. C. N. Armstrong, Dr. R. E. Jowett, Mr. R. S. Venters. *Leeds*, Dr. E. W. Jackson, Professor P. J. Moir, Dr. R. Watson, Dr. W. A. Hyslop, Mr. G. Whyte Watson. *Sheffield*, Professor J. G. McCrie, Dr. G. C. Wells-Cole, Dr. D. Macmillan, Mr. H. J. Malkin, Dr. R. J. Donaldson, Profesor A. W. Kay, Dr. C. S. O'Flynn. *East Anglian*, Dr. A. J. R. F. Johnson, Dr. J. V. Morris, Mr. M. W. B. Bulman, Dr. K. W. Mackenzie, Captain E. Murray Harvey, Professor A. Leslie Banks, Dr. K. J. Grant. *N.W. Metropolitan*, Sir Harold Boldero, Dr. Annis Gillie, Dr. H. Joules, Dr. J. B. S. Lewis, Dr. A. Staveley Gough, Miss E. Rickards, Mr. J. D. S. Flew, Miss K. G. Lloyd-Williams, Professor F. C. Wilkinson. *N.E. Metropolitan*, Dr. C. Allan Birch, Dr. Louis Comyns, Mr. D. F. Ellison-Nash, Dr. G. T. Hankey, Dr. T. Rowland Hill, Dr. J. A. Moody, Mr. R. W. Reid. *S.E. Metropolitan*, Mr. J. R. H. Turton, Dr. E. R. Boland, Dr. A. Talbot Rogers, Dr. L. C. Cook, Sir Wm. Kelsey Fry, Dr. Vernon F. Hall, Mr. J. H. Mayer. *S.W. Metropolitan*, Dr. G. W. Garland, Dr. T. P. Rees, Dr. C. J. Grosch, Professor W. J. Hamilton, Dr. L. Minski, Mr. A. L. Abel, Sir Geoffrey S. Todd. *Oxford*, Mr. G. T. Willoughby Cashell, Dr. A. W. Henderson, Dr. W. Ogden, Mr. J. A. Stallworthy, Dr. D. H. G. MacQuaide. *S.W. Regional*, Dr. R. G. Michelmore, Mr. H. L. Shepherd, Dr. G. S. Smith, Dr. L. W. Hale, Professor R. J. Brocklehurst, Mr. R. V. Cooke, Professor A. V. Neale. *Welsh Regional*, Dr. D. Kyle, Mr. I. Lewis, Dr. D. E. Parry-Pritchard, Mr. J. Howell Hughes, Dr. A. Trevor Jones, Dr. E. Wyn Jones, Mr. E. K. Roy Thomas, Dr. Morgan G. Williams. *Birmingham*, Dr. J. C. Heather, Professor T. McKeown, Dr. James J. O'Reilly, Dr. S. R. F. Whittaker, Dr. T. C. McKenzie, Professor C. F. V. Smout, Dr. J. H. Sheldon, Professor Sir Arthur P. Thomson. *Manchester*, Mr. T. S. Heslop, Professor W. I. C. Morris, Dr. S. C. Gawne, Dr. H. Pigott, Dr. S. Smith, Dr. R. W. Luxton, Dr. Miles Parkes, Emeritus Professor Sir Harry Platt. *Liverpool*, Dr. David Brown, Lord Cohen of Birkenhead, Sir Arthur Gemmell, Dr. S. Barton Hall, Professor A. B. Semple, Professor H. L. Sheehan. *Wessex*, Dr. A. J. Galbraith, Dr. I. A. Macdougall, Mr. H. H. Langston, Mr. R. W. Nevin, Dr. C. H. D. Bartley, Dr. L. H. D. Thornton.

West London Medico-Chirurgical Society

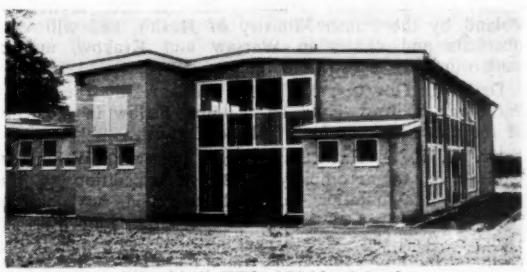
The following have been elected for the session of 1960 to 1961:

President, Mr. HARVEY JACKSON; *vice-presidents*, Dr. C. L. COPE, Mr. ALEX ROCHE, Mr. ARNOLD WALKER, Dr. ERIC HUDSON; *hon. treasurer*, Mr. G. B. WOODD-WALKER; *hon. librarian*, Dr. M. E. SHAW; *hon. secretaries*, Dr. IVOR WILSON, Dr. P. A. LAURENT; *council*, Dr. S. J. CARNE, Mr. JAMES KEMBLE, Dr. L. LAURENT, Dr. A. SPENCER PATERSON, Dr. A. B. STOUTE, Dr. J. D. W. WHITNEY.

School for Deaf Spastic Children

A specially built and equipped school for spastic children who are also deaf was recently opened by Sir ALEXANDER EWING in the grounds of the National Spastic Society's residential Wilfred Pickles School at Tixover Grange, Lincolnshire.

Instructions spoken by the teacher into a microphone will be re-radiated through a wire loop encircling each classroom under the floor and will be picked up by special receivers worn on the pupils' clothing. This will enable the children to be taught, whether at their desks or moving about, without wires impeding their movements. The school hall is also fitted with this system.



School hall, Wilfred Pickles School.

Grants, Gifts, and Bequests

The National Fund for Research into Poliomyelitis and Other Crippling Diseases has made grants of £14,620 for an electron microscope and an ultracentrifuge for research into muscular dystrophy in the department of neurology, the United Newcastle upon Tyne Hospitals; £13,305 to the Institute of Neurology, the National Hospital, Queen Square, for research in muscular dystrophy; £2,000 to develop a microfilm projector to enable those who cannot turn pages to read a book; and £150 for a study of the design of clothing for disabled men.

The Colonial Office has made three grants to the University College Hospital of the West Indies: £208,930 for a specialist block containing an ophthalmological section with an operating theatre, and ear, nose, and throat, dermatological, and orthopaedic sections; £162,618 for a new operating theatre block and for converting the existing operating room into a central sterilizing room; and £14,433 for an extension to the obstetrics and gynaecology block.

Mental Health Information

The World Federation for Mental Health is in the process of establishing a small clearing-house service for information on an international scale. The service will be particularly concerned with technical mental health projects in the Federation. Full details of existing or projected research studies should therefore be sent to the Scientific Director of W.F.M.H., 19, Manchester Street, London, W.1.

National Institute of Industrial Psychology

The National Institute of Industrial Psychology's Vernon Prize for 1960 has been awarded to Dr. R. B. BUZZARD, of the Medical Research Council's Industrial Psychology Research Unit, for his research into attendance and absence from work.

Territorial Army

Colonel G. M. WARRACK is to succeed Brigadier W. R. WARD as Adviser to the Director-General Army Medical Services on Territorial Army matters on December 1.

West Riding Edinburgh Graduates' Association

This graduate association would welcome new members. Information may be had from the Secretary, Mr. J. S. DAVIDSON, 1, Ashburnham Grove, Bradford, 9.

In Brief

A grant of £60,000, spread over the next five years, has been made by the Ernest Oppenheimer Memorial Trust towards establishing in Lusaka a multi-racial college of social service for Rhodesia and Nyasaland.

Sheffield University has created two new chairs—one of operative dental surgery, the other of dental pathology.

People in the News

Dr. JOSEPH BRAND, personal physician to H.H. the Sultan of Brunei and his household, has had the Insignia of the Most Honourable Order of the Crown of Brunei (D.P.M.B.), 2nd Class, conferred upon him.

Professor C. M. FLEMING, dean of the faculty of medicine, Glasgow University, is visiting Poland and Germany on behalf of the British Council. He has been invited to Poland by the Polish Ministry of Health, and will visit hospitals and clinics in Warsaw and Krakow, and a sanatorium in the Tatra mountains.

Dr. J. L. GOWANS, of the Sir William Dunn School of Pathology, Oxford, is to be the first Fellow in medicine of the new St. Catherine's College, Oxford.

Dr. G. F. C. HAWKINS, medical officer of Wellington College, is to accompany a British expedition to the castle of Maymum-Diz in Northern Persia, headquarters from 1090 till 1256 of the professional killers known as the Order of Assassins. The expedition hopes to penetrate the castle—a mountain four miles round and honeycombed with passages—for the first time since the Mongols starved it into submission over seven centuries ago.

London School of Hygiene and Tropical Medicine

Professor E. T. C. SPOONER has been appointed Dean of the School in place of the late Sir James Kilpatrick.

COMING EVENTS

1st International Congress on Medical Photography and Cinematography.—Dusseldorf, September 27–30. A free visit to the "photokina" in Cologne is planned for all Congress members. Final programme available after August 17 from Deutsche Gesellschaft für Photographie E.V., 49, Neumarkt, Cologne, to whom all inquiries should be addressed.

8th Mackenzie Industrial Health Lecture.—British Medical Association in conjunction with Association of Industrial Medical Officers. Dr. J. A. L. VAUGHAN JONES: "Rehabilitation—Theory and Practice," September 8, 2.15 p.m., Engineering Lecture Theatre, Lanchester Building, Southampton University, University Road, Southampton. Admission free.

6th International Convention on Nutrition and Vital Substances. — Baden-Baden, Germany, and Strasbourg, France, October 5–9. Details from the Secretary, International Society for Research on Nutrition and Vital Substances, 61, Bemeroder Strasse, Hannover-Kirchrode, Germany.

Society of Medical Officers of Health.—Reception in connexion with World Mental Health Year Conference, H.Q.S. *Wellington*, moored near Temple Underground Station, October 7, 7.30 p.m.

World Mental Health Year Conference.—"Community Mental Health Services": conference between Central Council for Health Education, College of General Practitioners, Royal Medico-Psychological Association, and Society of Medical Officers of Health, October 7–8. Details from these organizations.

NEW ISSUES

ARCHIVES OF DISEASE IN CHILDHOOD

Head Injuries in Children. John Burkinshaw.
The Importance of Accident-proneness in the Aetiology of Head Injuries in Childhood. M. W. Partington.
Abnormalities of Ventilatory Capacity in Children with Asthma and Bronchiectasis. L. B. Strang.
Measurements of Pulmonary Diffusing Capacity in Children. L. B. Strang.
Normal Standards for Single Breath Tests of Ventilatory Capacity in Children. Bryan Gandevia.
The Cerebro-ocular-renal Dystrophies: a New Variant. R. A. McCance, W. J. Matheson, G. A. Gresham, and J. R. Elkinton.
Sirenomelia and Monomelia with Renal Agenesis and Amnion Nodosum. A. D. Bain, M. M. Beath, and W. F. Flint.
Association of Sirenomelia with Potter's Syndrome. J. G. Bearn.
Aldrich's Syndrome: Familial Thrombocytopenia, Eczema and Infection. Ronald R. Gordon.
Effect of Corticotrophin on Hypothalamic Syndrome in Children. N. R. Butler, D. H. H. Pullon, and A. H. Snaith.
Serum Protein Pattern in Infants with Nutritional Disorders. B. L. Coles.
Effect of Triiodothyroacetic Acid on the Electrocardiogram in Cretinism. Thomas Stapleton, Chan Gunn, and Paul Gelpke.
Iron-deficiency Anaemia between 3 Months and 2 Years of Age, and a Comparison of Treatment with Ferrous Sulphate and Ferrous Fumarate. Chan Gunn, M. C. Islip, P. L. Masters, H. Erskine-Murray, C. A. Rigg, and T. Stapleton.
The Significance of One Umbilical Artery. Edith Faierman.
The "Stiff Man Syndrome" in a Boy. David Bowler.
Gout and Cerebral Palsy in a Three-year-old Boy. Ian D. Riley.
Calcification of the Digital Vessels in a Child with Rheumatoid Arthritis. Constance C. Forsyth.
Bilateral Trigger Thumb in Infants. Theodore James.
Paroxysmal Tachycardia in a Child Showing Stokes-Adam and Wolff-Parkinson-White Syndromes. Stanley de Silva.
Spontaneous Haemorrhage from the Internal Carotid Artery in a Child. Brian Webb and B. H. Pickard.
Blood Uric Acid Levels in Mothers and Infants at Birth. I. Kessel and W. M. Politzer.
Book Reviews.

Volume 35, No. 181. (Bi-monthly; £4 4s. annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, August 12

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. Howard Nicholson.

APPOINTMENTS

LIVERPOOL REGIONAL HOSPITAL BOARD.—A. McG. Stevenson, M.B., Ch.B., Whole-time Senior Casualty Officer to Bootle Hospital; A. J. Booth, M.B., Ch.B., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist giving maximum sessions to North Liverpool Group and St. Helens Hospital; D. H. Merrin, M.R.C.P.I., Whole-time Assistant Chest Physician to Cleaver Hospital.

LONDON COUNTY COUNCIL.—Helen E. E. Gunn, M.B., B.S., D.P.H., D.Obst.R.C.O.G., Whole-time Medical Officer in Public Health Department.

MANCHESTER REGIONAL HOSPITAL BOARD.—P. H. D. Lewars, M.B., B.S., F.D.S. R.C.S., Consultant Dental Surgeon, Wigan and Leigh, Salford and West Manchester Groups of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Shearer.—On June 20, 1960, at Western General Hospital, Edinburgh, Donald Angus MacMillan Shearer, M.B., Ch.B., of 47, Abercorn Terrace, Edinburgh.

Strain.—On June 20, 1960, at a nursing-home in Edinburgh, Arthur Charles Strain, M.D., formerly of West Hartlepool.

Verdon.—On June 18, 1960, at Nairobi, Kenya, Philip Verdon, B.Chir., M.R.C.S., L.R.C.P., Colonel, I.M.S., retired.

Wheeler.—On June 16, 1960, in hospital, Francis James Wheeler, M.R.C.S., L.R.C.P., of 4, Queen's Road, Southport.

Williams.—On June 21, 1960, at Oldchurch Hospital, Essex, John Ivor Williams, M.R.C.S., L.R.C.P.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Reactions to Ferrivenin and Lignocaine

Q.—*Severe, even fatal, reactions are a possibility when giving ferrivenin intravenously for anaemia or giving lignocaine 1% subcutaneously in midwifery. Faced with such a catastrophic situation, what would be the best way of dealing with it? Have steroids any part in such emergency treatment?*

A.—Ross[1] in a review of the literature and a survey of 802 patients given ferrivenin showed that reactions can be reduced by correct selection of patients and correct dosage. He emphasized the association of severe acute respiratory distress after ferrivenin with disorders of the pulmonary capillary bed. Severe respiratory distress occurred only in patients with mitral stenosis, chronic bronchitis with emphysema, severe kyphoscoliosis, or pulmonary tuberculosis, and in such patients doses must be 25–50 mg. (1.25–2.5 ml.) and given particularly slowly. Untoward reactions were relatively high in anaemia associated with chronic infection, rheumatoid arthritis, ulcerative colitis, or chronic nephritis, and here again initial doses must be 25–50 mg. Reactions were least in pure iron-deficiency anaemias—i.e., in pregnancy, puerperium, or following blood loss. The amount in a single injection rather than the total amount given is an important factor in avoiding reactions, and the dosage and technique advised by the makers must be adhered to rigidly.

The exact cause of the reactions remains uncertain. They are probably due to the fact that the iron-binding globulin of the serum is rapidly saturated and the excess iron consequently circulates in an unbound toxic form.[2] Nissim and Robson[3] have shown in mice that the injection of saccharated iron oxide is associated with precipitation of iron particles, particularly in the lung. The allergic hypothesis was not supported by Ross's clinical observations.

Ross treated reactions with rest, occasionally with sedatives, including morphine, and intravenous noradrenaline when vasomotor collapse persisted. It is doubtful whether steroids would be of value except possibly intravenously as treatment aimed at vasomotor collapse.

Reactions to lignocaine occur only when an overdose is given or when injected intravenously. The recommended dose is 20 ml., or 50 ml. if adrenaline has been added. No true allergic reaction to lignocaine has yet been recorded and the reactions that do occur are an extension of the drug's pharmacological action due to too large an amount entering the blood stream at once.

The treatment is essentially that of the signs as they appear; convulsions are treated by intravenous thiopentone and hypotension by a pressor drug such as methylamphetamine. Steroid therapy is not really indicated, but might possibly be used intravenously for persistent hypotension when other measures have failed.

REFERENCES

[1] Ross, I. P., *Lancet*, 1957, **2**, 77.
[2] Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1955, 2nd ed., p. 1465. Macmillan, New York.
[3] Nissim, J. A., and Robson, J. M., *Lancet*, 1949, **1**, 686.

Immunization of Children

Q.—*Is it still desirable to cease the immunization of children in the summer months because of the danger of provocation poliomyelitis?*

A.—In an ordinary summer period, when there is no excess of poliomyelitis in a district, inoculation should continue without interruption. "Schedule B" of immunizations, as recommended by the symposium on "Immunization in Childhood,"[1] could be followed. Combined prophylactics are advised in this schedule, but all alum-containing prophylactics are excluded.

When there is a local epidemic of poliomyelitis, *all* inoculations should preferably be stopped. There is perhaps one exception to this rule—namely, in the face of smallpox all vaccination risks must be accepted.

REFERENCE

[1] *Brit. med. J.*, 1959, **1**, 1345.

Habitual Abortion

Q.—*A woman aged 30 habitually aborts after 10–14 days. This has been attributed to faulty nidation, and she has been given ethisterone during the latter half of the menstrual cycles for the past six months. In spite of this she has aborted twice more at the usual 14 days. What else may be done?*

A.—Has it been proved, by examination of the material passed from the uterus, that all the episodes described have been abortions? Many women who allege early abortions suffer from no more than a delayed onset of menstruation. Such delay might even be encouraged by the administration of hormones premenstrually on the assumption that the endometrium is not being properly prepared for pregnancy. To substantiate a diagnosis it is necessary to demonstrate chorionic villi histologically; the finding of decidua is not conclusive. If, in fact, abortions have occurred, what is the basis for the diagnosis of faulty nidation? Did examination of the products of any of the conceptions show an abnormality in the foetus and membranes?

True early abortions are mostly caused by malformation of the embryo and its membranes, but whether this represents a genetic or environmental fault is unknown. There is as yet no known treatment for such cases.

Before another pregnancy, the patient in question should be fully examined to exclude any general ill-health. Even a minor degree of hypertension might be significant. Examination of the pelvic organs should also include hysterography to determine the shape of the corporeal and cervical cavities. Although uterine abnormalities are unlikely to cause abortion at such an early stage, it would be wise to exclude them. If no abnormality is found the patient might be encouraged to conceive again, but should not be given any treatment until it is established by a biological pregnancy test that she is definitely pregnant. An assay of the pregnanediol excretion during early pregnancy may also be helpful. Unless the results of investigations give a clear guide, treatment during pregnancy has then to be empirical, and consists in a reasonably restful life with avoidance of coitus. Some might also administer large doses of stilboestrol in the hope of improving uterine blood supply and hence endometrial receptivity. Such treatment is harmless, but its value remains unproved. Others might give progesterone, but this, again, has no established merit. Finally, if the patient should "abort" again, the products should be carefully examined to see if the ovum is "blighted," and if, in fact, there is any certain evidence of pregnancy.

Nystagmus in Alcoholic Intoxication

Q.—*What is the significance of lateral nystagmus in alcoholic intoxication?*

A.—Nystagmus is a complicated neurological phenomenon.[1] When testing for it the finger must be kept within the limits of binocular vision; otherwise the phenomenon often described as "nystagmoid jerks" may be elicited. True nystagmus is distinguished by more sustained movements of greater amplitude. The cause may be a lesion in the vestibular apparatus or in its peripheral or central pathways. Both barbiturates and alcohol may give rise to this type of abnormal ocular movement. To be certain that lateral nystagmus is due to alcohol or a drug the patient would have to be re-examined on a second occasion. However, in alcoholic intoxication other features are present, such as abnormalities in the size and reactions of the pupils, and most experienced police-surgeons regard it as a physical

sign which is helpful and reliable in confirming a diagnosis suggested by other clinical features. Absence of nystagmus does not indicate the absence of alcoholic intoxication. Goldberg[2] states that lateral nystagmus occurs at blood-alcohol concentrations of 80 to 100 mg. per 100 ml., and disappears at concentrations of over 300 mg. per 100 ml.

REFERENCES

1 Korkis, F. Boyes, *Recent Advances in Oto-laryngology*, 1958. Churchill, London.
2 *Proceedings of First International Conference on Alcohol and Traffic*, p. 263, 1951. Stockholm.

Lichen Hypertrophicus

Q.—*Will you please give me details of the current treatment of lichen hypertrophicus, including specific doses of steroids if they are really effective?*

A.—Response of hypertrophic lichen planus to treatment is often poor. Grenz-ray therapy and occlusive tar bandages ("coltapaste") are sometimes effective. The local injection of hydrocortisone acetate (12.5 mg. per ml.) produces temporary improvement. Systemic steroid therapy may clear the condition, but recurrence is common. One may give a limited course of A.C.T.H. starting with 20 units (gel) daily and gradually reducing over the course of six weeks, or prednisone by mouth starting with 5 mg. four times a day after meals for 10 days and then gradually reducing the dose over the period of the following month.

Morphine in Acute Paroxysmal Dyspnoea

Q.—*Could you explain the mechanism by which morphine acts in the treatment of acute paroxysmal dyspnoea? Is its effect due to its sedative action, its depressant effect on the respiratory centre, or has it an additional specific pharmacological effect?*

A.—The action of morphine in relieving acute paroxysmal dyspnoea due to left ventricular failure is not completely understood. The striking clinical improvement which usually follows its therapeutic use in these circumstances is probably the result of multiple factors. Certainly not the least of these is the relief of restlessness and anxiety, and it has been suggested that the beneficial effect of morphine in the treatment of acute dyspnoea of cardiac origin is simply due to the fact that the patient feels that breathing comes more easily rather than to any measurable improvement in respiratory function. The action of therapeutic doses of morphine on respiration is that the respiratory rate is first of all decreased, and for a time this effect is compensated for by an increase in the depth of respiration, and this slowing and deepening of respiration is clearly beneficial to the patient with the rapid shallow breathing of left ventricular failure. Morphine also depresses the respiratory reflexes and the cough reflex, which are excited in patients with acute paroxysmal dyspnoea. Morphine in small doses has little effect on the circulation, but it tends to cause hypotension and cutaneous vasodilatation, and, since the patient with paroxysmal cardiac dyspnoea frequently has hypertension and peripheral vasoconstriction, this action may also be beneficial. An action of morphine which is undesirable in these circumstances is its antidiuretic activity, but this is fortunately not very pronounced.

NOTES AND COMMENTS

Antithyroid Drugs and Cretinism.—Dr. B. J. O'DRISCOLL (Galway) writes: A doctor asks ("Any Questions?" May 28, p. 1674) if it is safe to give the antithyroid drug potassium perchlorate to a pregnant woman. The answer implies that it is quite safe if the maintenance dose is reduced by half. In my humble opinion this is most dangerous teaching and I feel it my duty to challenge it. As far back as 1953 a patient of mine whose thyrotoxicosis was well under control with the antithyroid drug thiouracil told me that she was pregnant. I knew Hughes[1] found that thiouracil given to pregnant rats caused goitre in the foetus. Therefore I was uneasy about leaving my patient on the drug. However, in spite of an intensive search of the literature, I could find no report that antithyroid drugs had injured a human foetus since Astwood[2] had introduced them into clinical medicine. Indeed, an article by Astwood[3] lulled me into a false feeling of complacency. In this article he recorded that 22 mothers who were taking thiouracil were all delivered of normal babies. He recommended that the maximum dose of thiouracil during the last three months of pregnancy should be 150 mg. per day. The knowledge that I was giving my patient only 100 mg. also consoled me. Therefore I continued to give the thiouracil to this woman during her pregnancy. To my disappointment, the baby that was born had a very large thyroid and it died the day after birth. While I was preparing an account of this case for publication Elphinstone[4] and Morris[5] both published accounts of cretinism in the babies of women who were taking antithyroid drugs. Indeed, following the publication of these articles, Macgregor[6] and Fraser and Fisher[7] wrote letters in which they tried to defend the use of antithyroid drugs in pregnancy. However, the arguments of neither were convincing. Therefore I thought it was not necessary to warn the profession about the dangers of using antithyroid drugs in pregnant women. Your expert says that there should be no interference with the thyroid function of the foetus if the maintenance dose is reduced by one half. Surely, if there is a maximum dose of potassium perchlorate which is safe for the foetus it should be possible to state it in milligrams. I fail to see how the size of the dose which the mother requires could have any mathematical relation to the amount that would be toxic to the foetus. May I suggest that the woman that your questioner mentions should have her goitre removed?

REFERENCES

1 Hughes, A. M., *Endocrinology*, 1944, **34**, 69.
2 Astwood, E. B., *J. Amer. med. Ass.*, 1943, **122**, 78.
3 —— *J. clin. Endocr.*, 1951, **2**, 1045.
4 Elphinstone, N., *Lancet*, 1953, **1**, 1281.
5 Morris, D., ibid., 1953, **1**, 1284.
6 Macgregor, A. G., ibid., 1953, **2**, 89.
7 Fraser, R., and Fisher, H. J., ibid., 1953, **2**, 89.

OUR EXPERT replies: There is the same difference of opinion concerning the treatment of thyrotoxicosis in pregnancy as there is concerning the treatment of thyrotoxicosis in the non-pregnant. There can be no doubt that surgical treatment of thyrotoxicosis can be safely undertaken in the pregnant woman; there is also no doubt, as was indeed demonstrated by the report of Astwood quoted by my critic, that the thyrotoxic woman can be safely conducted through her pregnancy, and without harm to the child, by the use of antithyroid drugs. Such treatment is in general use, and goitres in the newborn from this cause are rare. I have seen only a few of them and in no case has the baby suffered harm. It is, of course, impossible to state how much of an antithyroid drug can be given to a mother without producing a goitre in the newborn. There will presumably be an individual variation in the amount of the drug passing across the placenta and also in the amount which will interfere with the child's pituitary–thyroid axis.

Correction.—We much regret a printing error in some copies of the *Journal* in the statement by the Medical Advisory Council of the F.P.A. on "Use of Oral Contraceptives" (July 30, p. 380). The age range of volunteers for the trial should have read "25 to 35 years," *not* "25 to 24 years."

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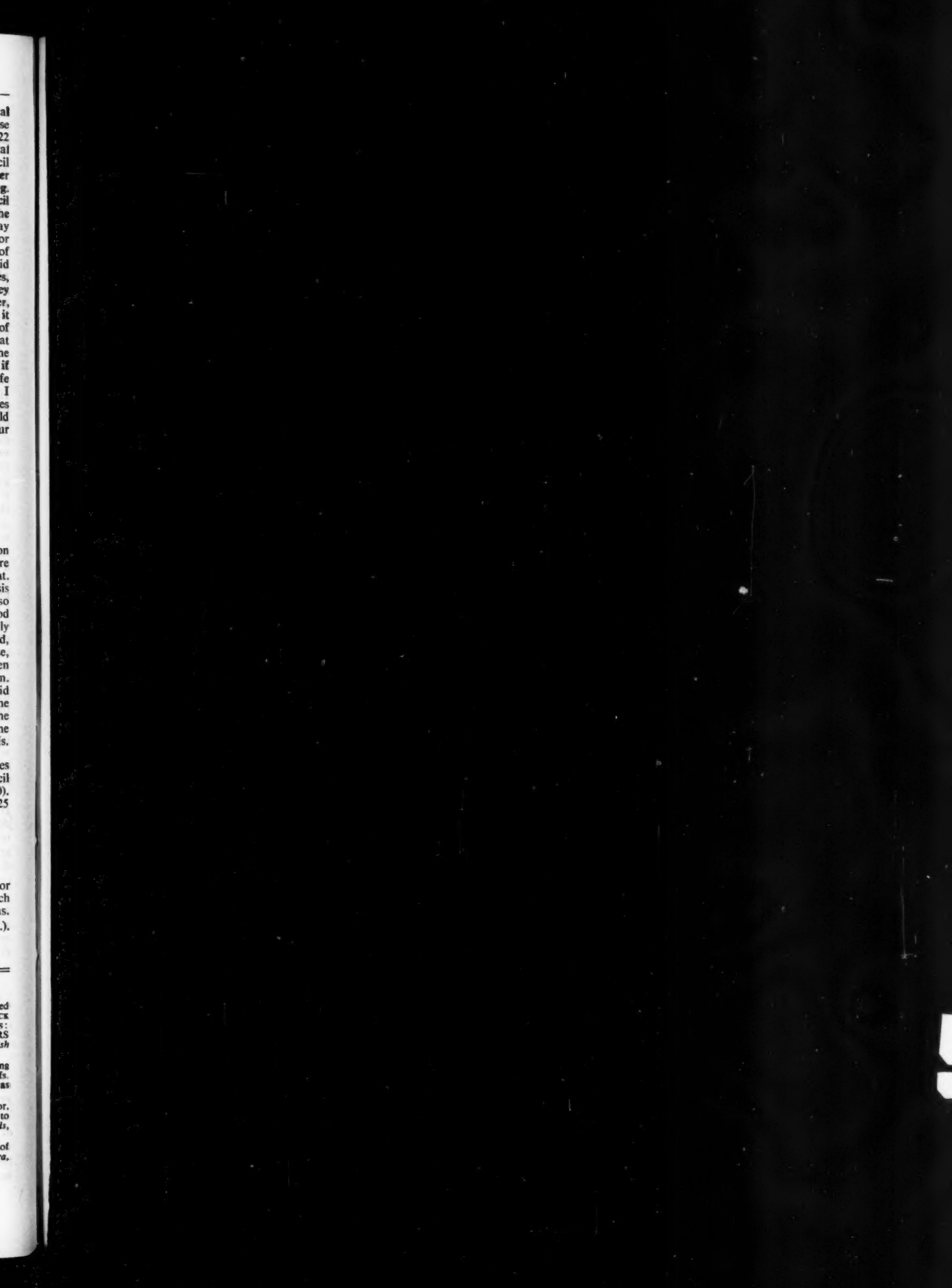
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